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Contents for January-February, 1956

DIAGNOSIS OF THE ALLERGIC STATE.
James M. Steele, M.D., F.A.C.A., Sayre, Pennsylvania 1

FUNGI AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASE.
XVI. Further Studies of the No. 33 Extraction Process: A Comparative Study of Several Dust Extracts.
William H. Browning, M.D., F.A.C.A., Shreveport, Louisiana 8
XVII. Comparison of the Allergenicity of a Sporulating and a Non-Sporulating Alternaria.
Homer E. Prince, M.D., F.A.C.A., Houston, Texas; *Morris A. Kaplan, M.D., F.A.C.A.*, Chicago, Illinois, and *Marie B. Morrow, Ph.D., F.A.C.A.*, Austin, Texas 15
XVIII. Air-Borne Soil Bacterial Allergy.
L. O. Dutton, M.D., F.A.C.A., El Paso, Texas 18
XIX. Bacteria, Actinomycetes, and Yeasts: Atmospheric Studies including a Dust Storm.
Marie B. Morrow, Ph.D., F.A.C.A., Austin, Texas; *George H. Meyer, M.A.*, Austin, Texas; *L. O. Dutton, M.D., F.A.C.A.*, El Paso, Texas, and *Homer E. Prince, M.D., F.A.C.A.*, Houston, Texas..... 21

ADJUNCTIVE PENICILLIN PROPHYLAXIS FOR BACTERIAL ALLERGY.
V. L. Szanton, M.D., F.A.C.A., Ansonia, Connecticut; *H. Cohen, M.D.*, and *H. G. Rapaport, M.D., F.A.C.A.*, New York, New York..... 30

REPEATED ANAPHYLACTIC REACTIONS IN A PATIENT HIGHLY SENSITIZED TO PENICILLIN.
K. J. Bierlein, M.D., Pittsburg, Kansas 35

SKIN ERUPTIONS FOLLOWING THE USE OF DIAMOX.
Maxwell Spring, M.D., Bronx, New York 41

TOPICAL USE OF PREDNISOLONE IN NASAL ALLERGY.
Jack R. Anderson, M.D., and *Henry D. Ogden, M.D., F.A.C.A.*, New Orleans, Louisiana 44

AILANTHUS GLANDULOSA POLLEN AS A CAUSE OF HAY FEVER.
J. Tas, Jerusalem, Israel 47

PRELIMINARY PROGRAM—Graduate Instructional Course in Allergy, April 15-17, 1956, and Twelfth Annual Congress, The American College of Allergists, Inc., April 18-20, 1956 49

DIPHEMANIL METHYLSULFATE CREAM PLAIN AND WITH HYDROCORTISONE IN THE TREATMENT OF VARIOUS SKIN DISEASES.
F. W. Wittich, M.D., F.A.C.A., Minneapolis, Minnesota 69

PREVENTION OF ACUTE ALLERGIC AND FEBRILE REACTIONS TO BLOOD TRANSFUSIONS BY PROPHYLACTIC USE OF AN ANTIHISTAMINE PLUS AN ANTIPYRETIC.
Chester C. Winter, M.D., and *George V. Taplin, M.D.*, Los Angeles, California 76

THE EFFECT OF CUPRIPORPHYRIN ON ANTIGENICITY AND PYROGENICITY OF INFLUENZA VIRUS VACCINE.
Mark D. Freeman, Henry T. Stanton, Jr., Robert D. Barnard and *Benjamin Goldman*, Mount Vernon, New York 82

NEUROPATHIC MANIFESTATIONS IN INFANTS AND CHILDREN AS A RESULT OF ANAPHYLACTIC REACTIONS TO FOODS CONTAINED IN THEIR DIETARY (Historical Document).
W. Ray Shannon, M.D., Saint Paul, Minnesota 88

EDITORIAL:
Twelfth Annual Congress 94

PROGRESS IN ALLERGY:
Gel Diffusion.
R. P. Wodehouse, Ph.D., Pearl River, New York 96

LETTER TO THE EDITOR 114

NEWS ITEMS 117

IN MEMORIAM 119

BOOK REVIEWS 120

Contents for March-April, 1956

ANTIGENIC ANALYSIS AND STANDARDIZATION OF TRICHINELLA EXTRACT BY GEL DIFFUSION.
Roger P. Wodehouse, Ph.D., Pearl River, New York..... 121

SKIN TESTS WITH BACTERIAL ANTIGENS IN RHEUMATOID ARTHRITIS.
Oscar Swineford, Jr., M.D., William P. Coleman, M.D., Charlottesville, Virginia, and *Austin T. Hyde, Jr., M.D.*, Rutherfordton, North Carolina..... 139

PSYCHIC FACTORS IN ALLERGY AND THEIR TREATMENT.
Harold A. Abramson, M.D., F.A.C.A., New York, New York..... 145

EVALUATION OF ANTI-ASTHMATIC MEDICATION.
Harold S. Tuft, M.D., F.A.C.A., and *Daniel M. Kraus, M.D.*, Denver, Colorado 152

IS POLLEN A CONTRIBUTING FACTOR IN THE SEASONAL INCIDENCE OF POLIOMYELITIS?
Daniel Leary, Harold C. Hodge, Ph.D., and *R. Plato Schwartz, M.D.*, Rochester, New York..... 157

RECURRENT COMA CAUSED BY RESPIRATORY FAILURE.
J. D. Charlton, M.D., F.A.C.A., J. B. Hickam, M.D., O. C. E. Hansen-Pruss, M.D., F.A.C.A., and *H. O. Sieker, M.D.*, Durham, North Carolina..... 162

THE EFFECT OF LONG TIME FEEDING OF A SOYBEAN INFANT FOOD DIET TO WHITE RATS.
H. W. Howard, Ph.D., R. J. Block, Ph.D., D. W. Anderson, Ph.D., and *C. D. Bauer, Ph.D.*, New York, New York..... 166

THE USE OF A NEW RESPIRATORY INDEX FOR THE EVALUATION OF XANTHINE DRUGS IN CHRONIC PULMONARY DISEASE
S. William Simon, M.D., F.A.C.A., Dayton, Ohio..... 172

A NEW ANTIHISTAMINE WITH MINIMAL SIDE EFFECTS.
Jerome J. Sievers, M.D., Sherman Oaks, California..... 181

CONTINUOUS STEROID HORMONE TREATMENT OF CHRONIC ASTHMA.
I. Cortisone and Hydrocortisone
Walter R. MacLaren, M.D., F.A.C.A., Pasadena, California, and *D. Edward Frank, M.D., F.A.C.A.*, Sun Valley, California..... 183

EVALUATION OF ISUPREL-FRANOL® IN THE TREATMENT OF THE ASTHMATIC ATTACK.
Aaron D. Spielman, M.D., F.A.C.A., New York, New York..... 194

HAY FEVER OR POLLEN POISONING (Historical Document).
Elias J. Marsh, M.D., Paterson, New Jersey..... 197

EDITORIAL
Properdin 205

PROGRESS IN ALLERGY
The Reporting of Drug Toxicity. Part I.
Ethan Allan Brown, F.A.C.A., M.R.C.S. (Eng.), L.R.C.P. (Lond.), Boston, Massachusetts..... 206

NEWS ITEMS..... 227

BOOK REVIEWS..... 229

Contents for May-June, 1956

A New Theory of Allergic Phenomena
M. G. Sevag, Ph.D., Philadelphia, Pennsylvania 233

Physiologic and Pathologic Allergy
Bela Schick, M.D. (Hon.) F.A.C.A., New York, New York 247

A Method of Reducing Reactions in Intravenous Pyelography with an Antihistamine
Maury D. Sanger, M.D., F.A.C.A., and *David E. Ehrlich, M.D.*, Brooklyn, New York 254

Effect of Injury To, and Electrical Stimulation of, Hypothalamic Areas on Anaphylactic and Histamine Shock of the Guinea Pig
Dr. Andor Szentiványi and *Dr. Judith Székely*, Budapest, Hungary 259

High Blood Eosinophilia in Food Allergy
Boen Swinny, M.D., F.A.C.A., San Antonio, Texas 261

Survey on Undergraduate and Graduate Education in Allergy:
Introduction to Survey
Horace S. Baldwin, M.D., New York, New York 262

Survey of Undergraduate Education in Allergy
Analysis of the Questionnaires Answered by the Deans of Medical Schools
Giles A. Koelsche, M.D., F.A.C.A., Rochester, Minnesota 265

Analysis of the Questionnaires Answered by Medical School Student Members of Alpha Omega Alpha Chapters
Giles A. Koelsche, M.D., F.A.C.A., Rochester, Minnesota 270

Report on a Survey of Graduate Education in Allergy
Richard A. Kern, M.D., Philadelphia, Pennsylvania 273

Survey on Education in Allergy
Robert A. Cooke, M.D., New York, New York 288

Progress in Allergy
Miscellaneous Review of Allergy—1955
Lawrence J. Halpin, M.D., F.A.C.A., Cedar Rapids, Iowa 291

In Memoriam 337

Papers of Interest 338

News Items 339

Book Reviews 341

Contents for July-August, 1956

THE FOUNDING OF THE SCIENCE OF ALLERGY
Bela Schick, M.D., (Hon.) F.A.C.A., New York, New York 343

CONSIDERATIONS OF SPECIAL INTEREST TO THE ALLERGIST ON THE COMPOSITION AND PRODUCTION OF POLIOMYELITIS VACCINE
M. Z. Bierly, Jr., M.D., Havertown, Pennsylvania 349

PNEUMONITIS AND ATELECTASIS OCCURRING IN THE COURSE OF ALLERGIC DISEASE
Lewis E. Abram, M.D., F.A.C.A., and *Jerome S. Frankel, M.D., F.A.C.A.*, Cleveland, Ohio 360

THE TREATMENT OF ALLERGIC DISEASES WITH THE STEROID HORMONES
William H. Lipman, M.D., F.A.C.A., Kenosha, Wisconsin 365

PSYCHOGENIC ECZEMA IN A CHILD
Harold A. Abramson, M.D., F.A.C.A., New York, New York 375

TREATISE ON ASTHMA (MAGALA FI-L-RABU) (Historical Document)
Maimonides (RaMbaM) 382

EDITORIAL
How Your College Works 384

PROGRESS IN ALLERGY
Headache
Henry D. Ogden, M.D., F.A.C.A., New Orleans, Louisiana 385

HOW YOUR COLLEGE WORKS
The Annals of Allergy 429

PAPERS OF INTEREST 432

LETTER TO THE EDITOR 434

IN MEMORIAM 435

NEWS ITEMS 436

BOOK REVIEWS 444

Contents for September-October, 1956

WASP VENOM ALLERGY AND IMMUNITY
Mary Hewitt Loveless, M.D., and *William R. Fackler, M.D.*, New York, New York 347

ALLERGY TO CASTOR BEAN MEAL
Roy A. Ouer, M.D., F.A.C.A., San Diego, California 367

A PARADOXICAL REACTION FOLLOWING THE ADMINISTRATION OF LAKED, INCUBATED, AUTOGENOUS BLOOD
Roger A. Lipton, M.D., Brooklyn, New York 370

PRESIDENTIAL ADDRESS
Lawrence J. Halpin, M.D., F.A.C.A., Cedar Rapids, Iowa 374

EDITORIAL:
Research in Allergy 381
Blisters: Poison Ivy or Phenyl Mercuric Acetate? 381
New Indian Drug Described 382

PROGRESS IN ALLERGY:
Food Allergy
Orval R. Withers, M.D., F.A.C.A., and *Ralph Hale, M.D., F.A.C.A.*, Kansas City, Missouri 384

HOW YOUR COLLEGE WORKS:
The Nominating Committee 457

PAPERS OF INTEREST 460

NEWS ITEMS 462

BOOK REVIEWS:
Experimental Tuberculosis Bacillus and Host. Editors: *G. E. W. Wolstenholme* and *Margaret P. Cameron* 465

Accidents Therapeutiques en Dermatologie. *Jacques Charpy* 465

The Practice of Psychosomatic Medicine as Illustrated in Allergy. *Hyman Miller, M.D.*, and *Dorothy Baruch, Ph.D.* 465

JAMA Clinical Abstracts of Diagnosis and Treatment. Selected by *Noah D. Fabricant, M.D.* 467

Collagen Diseases. *John H. Talbott, M.D.*, and *R. Moleres Ferrandis, M.D.* 467

Contents for November-December, 1956

A New Approach to the Treatment of Bronchial Asthma
I. S. Epstein, M.D., and *M. G. Sevag, Ph.D.*, Philadelphia, Pennsylvania..... 469

Controlled Studies of an Organic Iodide in Bronchial Asthma
Henry D. Ogden, M.D., F.A.C.A., and *John Salatich, M.D.*, New Orleans, Louisiana..... 480

Eczema of the Eyelids
Frederick H. Theodore, M.D., New York, New York..... 484

ACTH: Its Use by the Slow Intravenous Infusion Method for the Relief of Intractable Bronchial Asthma
Stephen D. Lockey, M.D., F.A.C.A., Lancaster, Pennsylvania..... 494

Environmental Climatologic Therapy in Bronchial Asthma
S. D. Klotz, M.D., F.A.C.A., and *Clarence Bernstein, M.D., F.A.C.A.*, Orlando, Florida..... 502

Molar Sodium Lactate in Acute Epinephrine-Fast Asthmatic Patients
J. S. Blumenthal, M.D., F.A.C.A., E. B. Brown, Ph.D., and *G. S. Campbell, M.D.*, Minneapolis, Minnesota..... 506

Anaphylactic Shock Due to the Use of Cosmetics
George R. Laub, M.D., F.A.C.A., Columbia, South Carolina..... 511

The Allergic Aspect of Recurrent Vomiting in Infants: Immunologic Feeding
Bert B. Schoenkerman, M.D., F.A.C.A., Milwaukee, Wisconsin..... 515

Preliminary Program—Postgraduate Course in Allergy and Thirteenth Annual Congress, The American College of Allergists..... 519

Editorials

The Association of Allergists for Mycological Investigations, Inc..... 541

Over-the-Counter Drugs..... 542

"The Whole Truth - - -"..... 544

Drug Evaluation..... 545

Penicillin in Milk..... 546

How Your College Works
The Credentials Committee..... 547

Letter to the Editor..... 551

Papers of Interest..... 552

News Items..... 554

Book Reviews..... 556

Index to Volume 14..... 559

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DIAGNOSIS OF THE ALLERGIC STATE

A Point Scoring System

JAMES M. STEELE, M.D.., F.A.C.A.
Sayre, Pennsylvania

THE diagnosis of allergy is often confusing and difficult; one of the sources of inaccuracy is lack of uniformity in our terminology. The original application of the term "allergy" by von Pirquet inferred simply a state of altered reactivity of the tissues. In this sense the concept is a very broad one, including such divergent phenomena as the lesions of adult tuberculosis, the skin rashes of scarlet fever and ivy poisoning, glomerulonephritis, rheumatic fever, and probably all of the somatic manifestations of emotional disturbance. This may be the preferable use of the term, but by common usage a more restricted application has evolved. To most of us today, the allergic state refers to that special type of allergy peculiar to humans, often associated with a familial trend and characterized by the presence of unique circulating antibodies (reagins). This might more accurately be designated as the atopic state, but a more effective semantic evangelist than this essayist will be required to bring about such a reform.

This confused situation was emphasized recently by an attempt at analysis of the allergy records in a general hospital. On this occasion, it was discovered that "allergy" was often diagnosed on the slenderest of recorded evidence; in some cases the facts seemed to point decidedly toward other mechanisms. In an attempt at clarification of this situation, a system was devised which we have designated a "point scoring system." It is the purpose of this presentation to describe this technique with an analysis of the aforementioned records.

In 1931 Rackemann[10] proposed a set of five criteria, later adding two more, for the determination of the presence of the allergic state (Table I).

From the Guthrie Clinic-Robert Packer Hospital, Sayre, Pennsylvania.

TABLE I. RACKEMANN'S POSTULATES

1. A characteristic symptom dependent on a characteristic local pathological condition.
2. A credible history of some other allergic symptom in addition to the presenting symptom.
3. A positive family history of allergy.
4. Positive skin tests.
5. Blood eosinophilia.
6. Response of symptoms to epinephrine.
7. A positive passive transfer reaction.

TABLE II. POINT SCORING SYSTEM

1. A characteristic symptom of allergy dependent upon local pathology explainable by allergic mechanism	1 point
If highly characteristic (such as strictly seasonal hay fever or nasal polyposis)	2 points
2. A history of either past or current allergic symptoms	1 point
If highly characteristic, as above	2 points
3. History of allergy in antecedents or descendants	
Unilateral	1 point
In antecedents, bilaterally	2 points
4. Relief of symptoms by adrenalin or antihistaminc drugs	1 point
or by repeated remission on elimination and recurrence on re-exposure to specific allergen	2 points
5. Blood eosinophilia in excess of 4 per cent	1 point
Secretion eosinophilia (nasal smear, et cetera)	2 points
6. Positive scratch tests	2 points
Positive intradermal tests	1 point
7. Demonstration of circulating antibodies (reagins) by passive transfer reaction of Prausnitz-Küstner	3 points

These have become canonized as "Rackemann's postulates" and have been adopted, with certain modifications, as a basis for our point system. Revision has been considered advisable because of two shortcomings in the original postulates: (1) obsolescence—there have been many developments in this area since 1931, such as the introduction of the antihistaminic drugs; and (2) absence of selective emphasis—for example, the first postulate would be satisfied equally well by recurrent diarrhea or epileptic seizures (both occasional allergic manifestations) as by nasal polyposis, where the incidence of allergic etiology runs very high.

Table II describes the point scoring system, with the number of points assigned to each factor. A perfect score of fifteen points is practically unobtainable, but we believe that a minimum of four points is essential for a definitive diagnosis of the allergic state, although in some circumstances three points may be highly suspicious. It should be emphasized that four points as an arbitrary minimum is merely our opinion; a revision upward or downward is permissible without vitiating the usefulness of the scoring system.

While nearly any tissue can on occasion become a "shock organ" in the reaction of hypersensitivity, there are certain organ systems that seem more vulnerable than others, and certain symptoms involving these organs which are highly characteristic of the allergic reaction. The commonest of these

TABLE III. CONDITIONS SUGGESTIVE OF ALLERGY

Respiratory:
Nasal blocking; watery rhinorrhea; recurrent "sinusitis"; frequent head colds; sneezing; nasal itching; wheezing; persistent cough; dyspnea; orthopnea.

Gastrointestinal:
Itching of the throat and palate; canker sores; angioedema; cyclic vomiting; irritable bowel syndrome; recurrent diarrhea; pruritus ani; pseudo-ulcer; pseudo-appendicitis.

Skin:
Acute urticaria; acute angioedema; "eczema" (particularly flexural); infantile eczema; (exclude contact dermatitis which is not an atopic manifestation).

Nervous:
Migraine; functional paralysis; Ménière's syndrome; "histamine cephalalgia"; some epileptiform seizures.

Cardiovascular:
Cardiac arrythmias; allergic purpura; polyarteritis.

Ocular:
Lachrymation and itching; eczema of lids; blepharitis; conjunctivitis; iritis; atopic cataract.

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manifestations are listed in Table III; some of them warrant special emphasis.

Itching of the nose, palate and throat associated with watery rhinorrhea or nasal blocking is so characteristic as to make one highly suspicious of allergy. The familiar "allergic salute" of children is a futile effort toward relief of this symptom. Brown[3] emphasizes the importance of itching in differentiating allergic rhinitis from hyperesthetic rhinitis due to other mechanisms. Balyeat[1] regarded itching of the eyes as almost pathognomonic of sensitization to some airborne substance, commonly pollen or orris root. Itching between the scapulae, over the sternum, or under the chin often precedes a typical asthmatic attack.

Sneezing is very common in nasal allergy, but also occurs in hyperesthetic rhinitis where no extrinsic allergens can be determined. This symptom as a characteristic peculiar to atopic rhinitis has probably been overemphasized.

Alternate nasal blocking and hydrorrhea occur in both atopic and non-allergic forms of hyperesthetic rhinitis; while suggestive, this sequence is not diagnostic of specific hypersensitivity.

Nasal polyposis is highly characteristic of allergy, and should be given a higher evaluation than less suggestive symptoms. Kern and Schenck[8] in surveying 345 cases of nasal polyposis found that an allergic history or other allergic manifestations were always present.

Periodicity of the aforementioned complaints, corresponding regularly to pollen seasons or other regularly recurring conditions, is highly suggestive of allergy. A well-authenticated history of remissions on elimination of a furry pet or a specific food, with invariable return of symptoms upon contact with the suspected agent, is very significant and at least twice as conclusive evidence as a single presenting symptom.

A personal history of other allergic manifestations lends added strength

to the likelihood of a presenting symptom's being due to allergy. The irritable bowel syndrome and complaints of fatigue are daily occurrences in the physician's practice; when associated with other conditions of probable allergic origin, an allergic component in these functional conditions may be considered. Conversely, the occurrence of asthma in an individual in the fourth decade or beyond with no history of any disorder conceivably allergic in origin makes one suspect an intrinsic basis for his trouble. Here, as in the first category, a strictly seasonal pollinosis or nasal polyposis rates two points.

In 1882 Salter[11] noted that 40 per cent of his asthmatic patients gave a family history of the same disease. This was confirmed in 1916 by Cooke and Vanderveer[4] who reported a positive family history in 48.4 per cent of their allergic patients, as contrasted with 7 per cent of nonallergic controls. Feinberg[6] observes that if allergy is present on both sides of the family, the incidence of allergy in the offspring is increased, with early and multiple manifestations. It was considered in this study that a bilateral family history was deserving of two points.

For many years epinephrine has been considered the drug of choice in symptomatic relief of allergic conditions, particularly asthma. It's principal effect is vasoconstriction but it also antagonizes the bronchoconstrictive influence of the vagus; these effects are more prompt and noticeable in the allergic mechanisms. While antihistaminic drugs are of doubtful value in asthma, other allergic manifestations usually obtain some degree of relief from their use. Since release of histamine (or H substance) is characteristic of many allergic processes, the relief of symptoms by histamine-neutralizing drugs is consistent with allergy, and we consider, as does Myers,[9] that such relief is indicative of an allergic component, thus rating one point in our schema.

If parasitism and leukemia can be excluded, blood eosinophilia is regarded as suggestive of an allergic mechanism, though it can be expected to disappear in the intervals between episodes. It is present in the nonsensitive as well as the hypersensitive group so that its demonstration can in no wise be interpreted as being pathognomonic of allergy. In fact, Cooke[5] finds it more common and of a higher degree in asthma of infective origin; in our system blood eosinophilia rates but one point.

Hansel[7] has described a technique for identification of eosinophils in nasal secretions; Tuft[13] regards this finding as highly characteristic of allergic rhinitis, as is also the finding of eosinophils in the asthmatic sputum. We assign two points to secretion eosinophilia.

Skin testing is a valuable diagnostic procedure if its limitations are realized. Intradermal tests are particularly prone to give misleading reactions, some of the reasons for which have been indicated in a previous publication.[12] Scratch testing is much less liable to give false positive reactions; for this reason it is felt that positive scratch tests merit two points while intradermals rate one.

The demonstration of circulating reagins by the Prausnitz-Küstner passive transfer technique is too cumbersome for routine use, but when available is so highly characteristic of allergy that we assign it three points in our schema.

ANALYSIS OF RECORDS

The clinic and hospital charts of 234 cases which had been diagnosed as allergic disease were reviewed. There were 106 females and 128 males. The primary diagnoses are summarized as follows:

Allergic rhinitis (non-seasonal)	65 cases
Allergic rhinitis (seasonal hay or rose fever)	98 cases
Bronchial asthma	60 cases
Allergic bronchitis	4 cases
Allergic conjunctivitis	2 cases
Atopic eczema	2 cases
Allergic sinusitis	1 case
Diagnosis unspecified	1 case

The age of these people at their first visit to the clinic for the allergic condition is as follows:

1-10 years	25
11-20 years	47
21-30 years	36
31-40 years	57
41-50 years	35
51-60 years	25
Over 60 years	5
Unspecified	2

The age of onset of allergic symptoms was recorded in 131 cases (56 per cent of the total):

1-10 years	55
11-20 years	28
21-30 years	23
31-40 years	11
41-50 years	8
51-60 years	6

In those 131 cases where the age of onset was known, eighty-three patients (63 per cent) were known to have developed their first symptoms before the age of twenty. If this percentage holds true of the whole group, 147 patients of the whole group should have reported for treatment before the age of twenty. However, only seventy-two (30 per cent) did so report during this period when treatment is most effectual.

A blood eosinophilia in excess of 4 per cent was reported in thirty-five cases, the highest being 21 per cent in an eighteen-year-old girl with nasal allergy and severe rheumatic heart disease. Eosinophilia of nasal secretion was recorded in only one case.

A family history of allergy was recorded in 127 cases (55 per cent), a bilateral history being present in eleven (5 per cent). The age of onset of

allergic symptoms in this group varied from two months to sixteen years, and the average number of diagnostic points was six.

Associated allergic conditions were reported as follows: asthma 23, eczema 30, seasonal hay fever 28, urticaria 23, nasal polyposis 19, perennial rhinitis 7, migraine 6, and others 8 cases. Ten patients reported relief of presenting symptoms by epinephrine and thirty-two cases by antihistaminic drugs. Scratch tests were positive in 151 cases and intradermals in fifty-seven more. There were twenty-six cases that showed only negative skin tests.

All cases showed at least one diagnostic point in our scoring system *viz*, a presenting symptom suggestive of allergy; the scores follow:

1 point	7 cases
2 points	10 cases
3 points	31 cases
4 points	58 cases
5 points	79 cases
6 points	37 cases
7 points	11 cases
8 points	1 case

Thus, slightly in excess of 20 per cent of these cases were diagnosed as "allergy" on evidence which we regard as less than the minimum requirement for such a diagnosis. It is interesting to note that the first twenty-two cases analyzed were all "allergic rhinitis," the records dating from February 1 to November 1, 1954, a time during which, due to a vacancy on the medical staff, the allergy department was unmanned. Of these twenty-two cases, 63.4 per cent were diagnosed on 3 points or less.

DISCUSSION

Feinberg[6] asserts: "At the very beginning one should ascertain that one is dealing with an allergic manifestation and the nature of the symptoms complained of should be recognized. This entails a differentiation of the complaint and conditions which simulate allergic manifestations." The rationale of this dictum should be obvious to any physician. As indicated by Bohrod[2] none of the histologic lesions seen in allergic states can be said to be pathognomonic, although several of them are highly characteristic; all "allergic" pathology is reproducible by other mechanisms. The physician who prematurely catalogues his patients as "allergic" on insufficient evidence does that patient a disservice in at least two ways; he tends to close the door to exploration of nonallergic factors, and he encourages that patient to embark on a time-consuming, costly, and often futile search up a blind alley for "allergens" which are too often phantoms.

While no clinician is entirely free from this error, our survey would make it appear that the nonallergist is three times as likely to drop into this pitfall as the trained allergist. We are of the opinion that a scoring system such as that presented, subject to modification if desired, but dis-

seminated and utilized by all clinicians, would tend to decrease inaccuracies in the diagnosis of the allergic state.

SUMMARY

1. An analysis of the records of 234 patients with a diagnosis of various allergic disorders is presented.

2. It would appear that in approximately 20 per cent of these cases the diagnosis of allergy had been made on the basis of insufficient recorded evidence.

3. A point scoring system is proposed and described which others may find useful as a gauge in the diagnosis of the allergic state.

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Submitted September 19, 1955

THIRD EUROPEAN CONGRESS OF ALLERGOLOGY

Florence, Italy, will be the site of the Third European Congress of Allergology, September 12-15, 1956. The subjects under discussion at this meeting will be: Genesis and Localization of Antibodies, Allergy and the Neuro-vegetative System, Factors of Increase of Allergic Conditions at the Present Time, The Mechanism of Delayed Reactions, and Allergological Classification and Terminology. During this congress it is hoped that a European Academy of Allergology can be founded. Professor Umberto Serafini of Florence is the General Secretary of the Organizing Committee for this congress.

FUNGI AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASE

The following four papers, which appear under the above heading, were presented as part of a symposium at the scientific meeting of the Association of Allergists for Mycological Investigation, Inc., held in Chicago, Illinois, April 27, 1955, in conjunction with the Eleventh Annual Congress of The American College of Allergists.

XVI. Further Studies of the No. 33 Extraction Process: A Comparative Study of Several Dust Extracts

WILLIAM H. BROWNING, M.D., F.A.C.A.
Shreveport, Louisiana

SEVERAL years ago a chemically precipitated dust antigen was introduced by Efron,[1] which proved to have definite diagnostic and therapeutic advantages over other available dust extracts at that time. It was soon made available commercially, and many of us began to use this dust extract almost exclusively. During the latter part of 1946, the supply of this extract became very limited, and some physicians found it necessary to go back to the older types of dust extract. One member of this group (H.E.P.) was confronted with this problem. Since he had had very satisfactory results with mold extracts using the No. 33 technique, and realizing the superiority of the chemically precipitated dust extract, he attempted to prepare a dust extract by the No. 33 technique. He was successful and found that the new extract possessed about the same diagnostic and therapeutic advantages as the commercial product. Since 1947, he has used it almost exclusively in his practice. Several members of the Association of Allergists for Mycological Investigations, Inc., have also used this dust extract on an experimental basis. It was for the purpose of affording further evaluation of extracts prepared by the No. 33 technique that the present study was undertaken.

Report of the Subcommittee for the Study of Dust Extracts Prepared by Various Techniques: William H. Browning (Chairman), Shreveport, Louisiana; Homer E. Prince, Houston, Texas; Richard L. Etter, Houston, Texas; Sam H. Sanders, Memphis, Tennessee; William C. Service, Colorado Springs, Colorado; W. Charles Gauntt, Austin, Texas; Lester L. Bartlett, Pittsburgh, Pennsylvania; Karl Figley, Toledo, Ohio; Morris A. Kaplan, Chicago, Illinois; Merle W. Moore, Portland, Oregon; and Ethan Allan Brown, Boston, Massachusetts.

Presented at the Scientific Session of The Association of Allergists for Mycological Investigations, Inc., Chicago, Illinois, April 27, 1955.

The expanded research activities of the Association necessitates a change in the general title of publications. The above title continues the series previously published under the general title, "Mold Fungi in the Etiology of Respiratory Allergic Disease," Articles I through XV.

TABLE I. IDENTIFICATION OF EXTRACTS AND DILUTIONS

Extract A	Hollister-Stier Crude Dust Extract (1:1) (Their Label 1:10)
Extract B	Acetone-Precipitated Hollister-Stier (1:50)
Extract C	Dust 4-25 (1:50) Prepared from Dust from a Pillow Renovating Plant by 33 Technique
Dust D	Dust 4-28 (1:50) Pooled Vacuum Cleaner Dust Furnished by Patients of H.E.P. and R.L.E. Prepared by 33 Technique.
Dust E	Endo Dust (1:40) (Lot 305273) Diluted to 1:50

Dilutions		Extract A	Extracts B, C, D & E
Concentrate	0.25 cc	1:20	1:1000
Diluent	4.75 cc		
1:20	0.50 cc	1:200	1:10,000
Diluent	4.50 cc		
1:200	0.50 cc	1:2000	1:100,000
Diluent	4.50 cc		
1:2000	0.5 cc	1:20,000	1:1,000,000
Diluent	4.5 cc		

Hollister-Stier Solution was furnished. Investigators were advised to make serial dilutions in a similar manner and use as a control against irritation from glycerin.

TABLE II. PUNCH OR SCRATCH TESTS

Sensitive	Neg.	One Plus	Two Plus	Three Plus	Four Plus
A. 1:1 Hollister-Stier Crude Dust	53	23	4	2	
B. 1:50 Hollister-Stier "AP" Dust	44	23	13	2	
C. 1:50 4-25 Dust	35	9	20	12	6
D. 1:50 4-28 Dust	36	16	20	6	4
E. 1:50 Endo Dust	64	12	5	1	
Allergic					
A. 1:1 Hollister-Stier Crude Dust	37				
B. 1:50 Hollister-Stier "AP" Dust	37				
C. 1:50 4-25 Dust	37				
D. 1:50 4-28 Dust	37				
E. 1:50 Endo Dust	37				
Non-Allergic					
A. 1:1 Hollister-Stier Crude Dust	16				
B. 1:50 Hollister-Stier "AP" Dust	16				
C. 1:50 4-25 Dust	16				
D. 1:50 4-28 Dust	16				
E. 1:50 Endo Dust	16				

METHODS

In November, 1954, the collaborators in this study were supplied with concentrates of five dust extracts labeled only with coded letters "A to E." The investigators were not given the key to the labeling, which was kept secret and in the files of one of us (H.E.P.). Table I reveals the identity of the dust extracts, their sources and dilutions. Those participating in the study were instructed to use the concentrated extracts for punch or scratch tests and to make serial dilutions from 1:20 to 1:20,000 for intracutaneous testing. Such dilutions resulted in actual testing strengths of 1:1,000 down to 1:1,000,000 for all of the precipitated extracts. For the crude extracts, the testing strength was from 1:20 to 1:20,000.

The collaborators in this study represent many sections of this country which may or may not be important in the evaluation of the efficiency of a dust extract.

TABLE III.

Clinically Sensitive to Dust	Dilution I 1:20,000 A 1:1,000,000 BCDE					Dilution II 1:2,000 A 1:100,000 BCDE					Dilution III 1:200 A 1:10,000 BCDE					Dilution IV 1:20 A 1:1,000 BCDE				
	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+
A Hollister-Stier 1:1 Crude Dust	81 90.2% 74	5	1	1	1	81 80.2% 65	10	2	1		78 52.6% 41	19	9			77 22.1% 17	13	24	8	
B Hollister-Stier 1:50 "AP" Dust	79 86.1% 68	9		2		78 67.9% 53	15	4	2	1	76 36.8% 28	17	17	5		76 18.4% 14	17	11	12	5
C 4-25 Dust 1:50 33 Technique	75 72.0% 54	10	6	2	3	75 54.7% 41	9	10	8	2	75 40.0% 30	7	8	13	3	74 17.4% 13	15	9	10	8
D 4-28 Dust 1:50 33 Technique	74 74.3% 55	5	6	4	4	74 55.4% 41	15	11	3	2	74 32.4% 24	14	9	15	4	74 21.6% 16	9	10	10	13
E Endo Dust 1:50	77 87.0% 67	9		1		77 74.0% 57	14	1	1	2	76 55.3% 42	13	10	2		75 40% 30	6	13	9	

PUNCH OR SCRATCH TESTS

Eighty-two subjects, clinically sensitive to dust, were tested by the punch or scratch method. Some of the subjects had been treated with dust extracts, but the type of extract used for treatment and the duration of treatment were not indicated. This could conceivably have some effect on the result of this study. It should be pointed out also that the extracts were not tested on a sufficient number of subjects to indicate an absolute efficiency index.

Table II shows the consolidated results of punch and scratch tests. It will be noted that Hollister-Stier Crude Dust Extract (1:10 their label), or Extract A, gave fifty-three negative tests (64.6 per cent) and twenty-nine positive reactions; twenty-three of these were one plus reactions, four were two plus reactions and two were three plus reactions. The Acetone-Precipitated Hollister-Stier Extract (1:50), or Extract B, gave forty-four negative tests (53.7 per cent) and thirty-eight positive reactions; twenty-three of these were one plus reactions. Dust Extract 4-25 (1:50), Extract C, prepared by the 33 technique from dust from a pillow-renovating plant, gave thirty-five negative tests (42.7 per cent) and forty-seven positive reactions, and only nine of these were one plus reactions. Dust Extract 4-28 (1:50), Extract D, prepared by the 33 technique from pooled vacuum cleaner dust furnished by patients, gave thirty-six negative tests (43.9 per cent) and forty-six positive reactions; sixteen of these were one plus reactions. Endo dust (1:50), Extract E, gave sixty-four negative reactions (78 per cent) and only eighteen positive reactions; twelve of these were one plus reactions. The extracts were tested on thirty-seven allergic subjects who were not clinically sensitive to dust and on sixteen nonallergic subjects. All of the tests were negative. Certainly the extracts are not irritants.

One plus reactions have been stressed because in studying the reports of the various investigators the impression was gained that some of the one plus reactions had little or no clinical significance. Take Extracts C and D for example. The total number of positive and negative reactions are very similar, but there is quite a difference in the types of positive reactions. Extract C had only nine one plus reactions compared to sixteen from Extract D. In three and four plus reactions, Extract C gave eighteen positives, whereas, Extract D gave only ten positives. It is obvious that Extract C is the more efficient of the two extracts and, since they were prepared in a similar manner, the source of material for preparing the extracts must account for the difference in the two extracts.

It is difficult to explain the large number of negative tests on a group of subjects clinically sensitive to dust. It is possible that treatment has had some effect on skin sensitivity, accounting for some of the negative tests. It is also possible that considerable time has elapsed since some of the subjects had had clinical manifestations and during this interval the

TABLE IV.

Allergic No Dust Sensitivity	Dilution I 1:20,000 A 1:1,000,000 BCDE					Dilution II 1:2,000 A 1:100,000 BCDE					Dilution III 1:200 A 1:10,000 BCDE					Dilution IV 1:20 A 1:1,000 BCDE				
	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+
A Hollister-Stier Crude Dust 1:1	36	1				34	2				32	2		1		31	3			
B Hollister-Stier "AP" Dust 1:50	36	1				33	3	1			30	2	3		1	29	1	3	1	
C 4-25 Dust 1:50	34	3				32	3	2			30	2	2	2	1	29	2	3		
D 4-28 Dust 1:50	32	3		1		30	4	1	1	1	30	1	4		1	29	1	2	1	1
E Endo Dust 1:50	36	1				34	33				31	3	2			29	1	4	1	

TABLE V.

Non-Allergic	Dilution I 1:20,000 A 1:1,000,000 BCDE					Dilution II 1:2,000 A 1:100,000 BCDE					Dilution III 1:200 A 1:10,000 BCDE					Dilution IV 1:20 A 1:1,000 BCDE				
	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+	Neg.	1+	2+	3+	4+
A Hollister-Stier Crude Dust 1:1	16	1		1		15	2				14	2	1			10	3	2	1	
B Hollister-Stier "AP" Dust 1:50	17	1				15	3				13	3	1	1		10	1	4	1	
C 4-25 Dust 1:50 33 Technique	16	2				14	3	1			13	2	2			9	4	3		
D 4-28 Dust 1:50 33 Technique	16	2				15	2	1			10	4	2	1		10		4	1	
E Endo Dust 1:50	17	1				16	2				14	4				12	3	2		

skin had lost its sensitivity, accounting for more negative tests. It is also possible that some of the patients were not clinically sensitive to dust but had been considered as such on the basis of tests with an irritant or unreliable dust extract.

Considering these groups, it is quite evident that Extract C, or Dust 4-25, (1:50) prepared by the 33 technique from dust from a pillow-renovating plant is the most efficient. Extract D, or Dust 4-28, (1:50) also prepared by 33 technique, is second best. Extract B, or Hollister-Stier Acetone-Precipitated, (1:50) is third best.

INTRACUTANEOUS TESTS

The results of tests on subjects clinically sensitive to dust are recorded in Table III. The extracts are identified and the dilutions for testing are indicated. The negative tests and positive reactions are recorded. The number in the upper right corner of each block indicates the total number of test subjects, including those which have been dropped because of a strong reaction in a weaker dilution. The per cent in the negative column refers to negative tests or non-reactions.

In Dilution I, it is apparent that Extracts A, B and E gave relatively few of the stronger reactions. It is interesting to note that in a comparative study of Extracts C and D in Dilution I, our weakest testing dilution, Extract D gave more two, three and four plus reactions than Extract C. This is just the opposite of what was seen with these two extracts in scratch or punch tests. I can offer no explanation of this.

In Dilution II, again it is apparent that Extracts A, B, and E gave relatively few of the stronger reactions. But in the comparative study of Extract C and D, the situation is reversed with Extract C giving the stronger reactions, just as it did in the scratch tests.

Going to the next strongest dilution, Dilution III, a peculiar situation has developed. The percentage of negative tests has become very close for Extracts B, C and D. However, if negative tests are combined with one plus reactions, the picture is changed. I have previously mentioned that in all probability, the one plus reaction as read by some of the collaborators has very little significance. Using the combined figures, Extract B would now be 59.2 per cent. Extract C becomes 49.3 per cent and Extract D, 51.3 per cent.

The strongest testing strength, Dilution IV, shows Extracts A, B, C and D to be of about equal potency, but from my observations and from the comments made by others in this study the extracts in this dilution are irritants. I observed most of my test subjects twenty-four hours after tests were performed and found that delayed or irritant reactions were present. These reactions were visible for several days. Consequently, I do not believe the results reported have any significance. One result reported by (S.H.S.), but not recorded in Table III, is quite significant. It was a mild Arthus phenomenon to Extracts C and D.

It appears from the foregoing that when Dilutions I, II, and III are considered, the two extracts prepared by 33 technique are of about equal potency and are much more efficient than other extracts used in this comparative study.

The extracts were also tested on a group of allergic subjects who were not clinically sensitive to dust and on a group of subjects who presumably did not have any allergic manifestations. The results are recorded in Tables IV and V. There were quite a few one plus reactions recorded, but the comments previously made about one plus reactions apply here. The stronger reactions in Dilutions I, II and III are within the limits of normal expectancy.

One case which had previously given positive skin reactions and which had not had clinical symptoms was reported by one investigator (E.A.B.). Similar cases probably account for the other reactions.

COMMENTS

A comparative study of two dust extracts prepared by the 33 technique and three dust extracts available commercially has been made by a group of investigators representing many sections of the country. It appears from this study that both of the extracts prepared by the 33 technique are definitely superior to the commercial extracts. It appears from this study that the source of material for the production of the extract is important and a much larger study of this factor should be made. From this particular study there did not seem to be any appreciable difference in the efficiency of the extracts in different parts of the country, but a more extensive study is indicated.

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Submitted September 14, 1955
1717 Marshall Street

AMERICAN-HUNGARIAN MEDICAL ASSOCIATION

Dr. Hans Selye of Montreal, Director of the Institute for Experimental Medicine, delivered the 1955 Semmelweis lecture, "Recent Progress in the Study of Stress," at the annual Semmelweis meeting of the American-Hungarian Medical Association, Friday, December 9, 1955, at Hosack Hall, New York Academy of Medicine. At this meeting, Dr. Selye was presented with the Ignatz Semmelweis Medal, awarded annually by the American-Hungarian Medical Association to an outstanding scientist of Hungarian origin. Previous recipients have included Drs. Szent-György and Bela Schick.

FUNGI AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XVII. Comparison of the Allergenicity of a Sporulating and a Non-Sporulating Alternaria

HOMER E. PRINCE, M.D., F.A.C.A., Houston, Texas; MORRIS A. KAPLAN, M.D., F.A.C.A., Chicago, Illinois and MARIE B. MORROW, Ph.D., F.A.C.A., Austin, Texas

SOME time ago one of our experiments required *Alternaria tenuis* from sources other than our own stocks, and we obtained one such culture from the American Type Culture Collection. This mold presented characteristics of *Alternaria tenuis,* except that on all media we used it failed consistently to sporulate. Upon checking with the curator of the American Type Culture Collection, we learned that the culture we had received had never sporulated on artificial media, but that it did produce enough spores on Melilotus stems to insure its identity.[3]

In considering what we might be able to do with this unusual culture of *Alternaria tenuis* which produced only mycelium, we were reminded of an earlier unsuccessful effort some twelve years ago at separating spores from mycelium for experimental extraction of the resulting pellicle fractions. It occurred to us that with reliable extracts, such as could be prepared by our 33 technique, we might profitably compare the allergen derived from this Alternaria mycelium with a corresponding antigen prepared from the usual sporulating *Alternaria tenuis.* Obviously, differences in the reactivity of the respective antigens would be interesting in view of previous claims[1,2] that spores rather than mycelium are the major sources of fungus allergenicity.

METHODS AND RESULTS

In arranging this experiment, we prepared a type 33 extract (No. 33-255) from this non-sporulating *Alternaria tenuis* for comparative skin testing with two different extracts (Nos. 33-212 and 33-238) made from our stock culture of a typically sporulating *Alternaria tenuis.* Although the three extracts were not made simultaneously, we felt that for the purpose of this experiment any differences in potency due to aging of the glycerinated antigens would be negligible.

Direct Tests.—Thirty-two Alternaria sensitive patients were tested both by punch (scratch) and by intradermal titration techniques. Nine of these

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Presented by Dr. Morris Kaplan at the Scientific Session of The Association of Allergists For Mycological Investigations, Inc., April 27, 1955.

From the Plant Research Institute, The University of Texas, in collaboration with The Association of Allergists For Mycological Investigations, Inc.

TABLE I.

Patient		Scratch (punch) 1/50		Intradermal Titration 1/1,000,000		1/100,000		1/10,000		1/1,000	
		NS	S	NS	S	NS	S	NS	S	NS*	S**
1		−	−	−	−	±	±	±	+	+	+
2	T	+	+	+	+	++	+++	+++	+++		
3	T	±	±	−	+	+	++	++	+++		
4	T	++	++	++	++	+++	+++				
5	T	−	±	−	−	−	±	±	+		
6	T	−	−	−	−	±	−	+	±	+	+
7	T	+	+	−	−	−	−	+	+	+	+
8	T	+	+	+	+	++	++	+++	+++		
9	T	±	±	−	−	±	+	+	++	++	++
10	T	±	±	−	−	±	+	++	++	++	++
11	T	±	+	−	−	±	+	+	+	+	+
12	T	±	±	−	−	±	−	+	+	+	+
13	T	+	+	−	−	−	−	±	±	+	+
14	T	+	+	−	−	−	−	±	+	+	+
15	T	+	+	+	+	++	++	++	++	+++	+++
16	T	+	+	+	+	++	++	++	++	+++	+++
17	T	+	+	−	−	±	±	+	+	+	+
18	T	+	+	−	−	±	±	±	+	+	+
19	T	+	+	−	−	±	+	+	+	+	+
20	T	+	+	−	−	±	+	+	+	+	+
										M.K.	
		NS	S	NS	S	NS	S	NS	S	NS*	S***
21		+	+					+	+		
22		+	++++			+	+	++	++++		
23	T	+±	++	+	−	++	++				
24	T	++±	+	±	+	++±	++				
25	T	+	++			+	++	++	+++		
26		+±	++					+	+	+++	++±
27		+++	++±			±	+				
28	T	+++	++±	+	±	++±	++	+++	++±		
29		++	+++			+++	+++				
30		++	+++±			+±	++	+±	++		
31	T	++±	+					++	±	++	++++
32		++	+++			+	++	++	++++		
										H.E.P.	

*NS—non-sporulating Alternaria tenuis No. 33-255.
**S—ordinary sporulating Alternaria tenuis No. 33-238.
***S—ordinary sporulating Alternaria tenuis No. 33-212.
T—patient previously treated with Alternaria.

patients had no previous treatment, while the remaining twenty-four had received a variable number of injections of Alternaria antigen. The results of these tests are shown in Table I. No constant differences in the reactivity of the non-sporulating Alternaria extract in comparison with the extracts of sporulating Alternaria are revealed by either the punch (scratch) or intradermal titration tests.

In Vivo Neutralization Tests.—Serum from an untreated patient sensitive to *Alternaria tenuis* was preserved with 1:100 volume of 1 per cent aqueous merthiolate solution (Lilly), making the final merthiolate concentration 1:10,000. This serum was injected intradermally in amounts of 0.10 cc in two rows of four sites each on the back of a suitable recipient. Another site was prepared on the outer aspect of each upper arm, to serve as final controls at the conclusion of the tests. Forty-eight hours later, the row of prepared sites on the left was tested intradermally with 0.05 cc of 1:1,000 sporulating *Alternaria tenuis* type 33 and the row on the right was similarly tested with the non-sporulating Alternaria. An appropriate control was made at the same time in nonsensitized skin with each antigen,

TABLE II.

Site No.	Sites Prepared 1/21/55				Test with 0.05, 1/1,000			
	1/24/55	1/25/55	1/26/55	1/27/55	1/24/55	1/25/55	1/26/55	1/27/55
1	S*+++	S+++	S+	S−	NS**+++	NS+++	NS+	NS−
2	S+++	S+++	S+	NS±	NS+++	NS+++	NS+	S−
3	S+++	S+++	S+	N−	NS+++	NS+++	NS+	NS−
4	S+++	S+++	S+	NS±	NS+++	NS+++	NS+	S−
			Control S+++				Control NS+++	

S*—sporulating Alternaria tenuis No. 33-238.
S**—non-sporulating Alternaria tenuis No. 33-255.

according to the usual Prausnitz-Küstner technique. After twenty-four hours the sites were similarly tested and found to be quite reactive; the next day they still reacted slightly on retesting. On the fourth day, the first and third sites in each row were tested with the homologous Alternaria with negative results, whereupon the second and fourth sites were tested with the respective heterologous extracts. All reactions were negative, suggesting cross-neutralization had been effected within the limits which could be determined by this technique. At the conclusion of the above testing, the final control sites on the outer aspect of each arm were found to be reactive to each Alternaria. Results of these tests are shown in Table II. The *in vivo* neutralization experiment was repeated with similar results.

DISCUSSION

It is obvious from these studies that Alternaria mycelium is allergenic. If the Alternaria antigen obtainable from aliquot portions of the sporulating and non-sporulating culture material could be subjected to a mathematical factor on the basis of relative biological reactivity, the total amount of major antigen from each source could be estimated. Unfortunately, the precipitation technique employing water miscible organic solvents, such as acetone, for concentration of allergenic extracts is not strictly a quantitative procedure. It cannot be concluded, therefore, that the presence or lack of sporulation modifies the total amount of allergen in *Alternaria tenuis,* since the 33 type antigens seemed to possess about the same major allergens, without appreciable differences in concentration.

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808 Carolina St.
Houston, Texas (Dr. Prince)

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FUNGI AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASE

XVIII. Air-Borne Soil Bacterial Allergy

L. O. DUTTON, M.D., F.A.C.A.
El Paso, Texas

IN previous publications my interest in the possibility that soil bacteria are potential allergens has been noted. My observations in this field have extended over a period of about ten years. Interest in this group of probable allergens was stimulated by a search for the causative agents responsible for acute exacerbations of hay fever and asthma during the occurrence of the typical dust storms of the Southwest. It was noted that many allergic patients tolerated these storms with no more discomfort than the usual nonallergic individual, while some experienced marked flareups of symptoms. Many efforts at identifying an allergic factor in these dust clouds resulted in complete failure, until the conception that bacteria might be the responsible factor was brought to my attention.

METHODS

It was thought that methods similar to those employed in mold studies would be appropriate. Accordingly, plates of plain nutrient agar were exposed for fifteen minutes and incubated at room temperature and at incubator temperature. Colonies were counted after twenty-four and forty-eight hours, and the predominant nonsporulating organisms were transferred to suitable media for vaccine production. After sufficient growth was obtained, these organisms were suspended in heavy concentration in normal saline containing 0.5 per cent phenol. This vaccine was diluted 1:10, 1:100, 1:1,000. Skin tests were done by the intradermal route using 0.02 cc in the usual manner. It was found that immediate wheal positive skin reactions were obtained within ten to thirty minutes, and that delayed tuberculin-type reactions did not occur.

RESULTS

The observations made over the years following this technique have given me certain definite impressions:

1. There is a strong correlation between positive skin reactions and the history of acute episodes, apparently attributable to dust storms.

2. Significant improvement in these patients could be made by utilizing this vaccine in treatment, employing it as one would employ pollen antigen; that is, by beginning with very small doses, usually .05 cc of a

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1:1,000 dilution, and gradually increasing to the 1:10 dilution or the full strength.

3. It was possible to produce an exacerbation in symptoms in the absence of dust clouds by overdosage.

4. On a few occasions it has been possible to demonstrate circulating antibodies by passive transfer.

CASE REPORTS

The following case reports illustrate how this approach has helped in the solution of specific problems.

Case 1.—E. H. B., aged forty-five, was first seen in 1943 and has been under my observation since. She was an extremely allergic individual with a long history of asthma and arthritis, the asthma and hay fever having begun in childhood. She was very co-operative, but none of our efforts with diet, pollen and house dust desensitization, search for unusual allergens, administration of respiratory vaccines, and other therapy interrupted her usual series of hospitalizations with severe asthma. This patient gave a persistent and unmistakable history of acute exacerbations due to dust storms. In 1948 she was tested with the 1:100 dilution of the air-borne bacteria, with a resulting strong four plus immediate skin reaction. This antigen was added to her therapeutic program. Some improvement was made, although it was not entirely satisfactory. The following year, a collection of dust from her vacuum cleaner was cultured for its bacterial content and a vaccine prepared. Different strains of organisms were found than the usual strains found from air isolation. Reactions were positive to this antigen, and it, too, was added to her therapeutic program. Within three or four months she began to make a steady improvement, and although we have not been able entirely to eliminate all hay fever and asthma symptoms, we have improved her general condition about 75 per cent, and have entirely eliminated attacks of status asthmaticus. She has had no further hospitalization or asthma since that time, in contrast to the previous three to six weeks periods of hospitalization occurring three or four times yearly.

Case 2.—J. K. L., aged twelve, was first seen in April, 1952, with an almost lifetime history of severe asthma which had hospitalized her repeatedly and caused her to be sent from the Texas Gulf Coast to the drier climate of El Paso for possible climatotherapy. Between April and September, 1952, she had three hospitalizations for status asthmaticus, which fortunately responded promptly to temporary therapeutic measures. In September we tested her to the air-borne bacterial antigen, and she responded with a strong four plus reaction to the 1:1,000 dilution with an almost immediate severe exacerbation of asthma. After the subsidence of this reaction, which required several days, therapeutic doses were begun with a 1:100,000 dilution. Since that time, this child has tolerated dust storm exposure with only minimal asthma, and she has now gone for long periods without recurrence of severe asthma. Although she has been treated with other antigens, these are essentially duplications of antigens given her over the previous year.

Case 3.—J. F. K., aged fifty-eight, was seen first in February, 1955, with nasal blocking and drainage, productive cough, and a history that these symptoms occurred only when dust storms were prevalent. The date of the first examination was during a period of heavy dust clouds. The nasal smears were essentially 100 per cent eosinophilic. Although by skin test he showed many positive tests to pollens

and animal epidermals, and a few to foods, the largest skin reaction by far was to a 1:100 dilution of the air-borne bacterial antigen, which was recorded as four double plus. The other air-borne antigens to which he reacted were not yet in season. Treatment was begun with a bacterial antigen only, in dilutions of 1:10,000. Improvement was noted after two weeks of therapy, and he has since withstood the extremely heavy dust clouds that have occurred this spring without appreciable difficulty.

COMMENTS

It is my impression that an antigen of air-borne bacteria has been therapeutically effective in these three widely divergent cases. It is difficult for us to find patients, as in Case 3, who give such a clearcut history of rhinitis incident to dust storm exposure and at no other time. We therefore feel that Case 3 is especially significant in indicating that allergic rhinitis may occur due to air-borne bacterial exposure, and that therapy with a desensitizing technique is effective.

If these observations are correct, there is a whole new field of bacterial allergy to be studied. It appears that much the same task is ahead in this field which has been so vigorously carried out during the past twenty years in regard to air-borne fungi.

616 Mills Building

Submitted September 14, 1955

AMERICAN FOUNDATION FOR ALLERGIC DISEASES

The American Foundation for Allergic Diseases is launching a campaign to raise $1,100,000 to carry out a three-point program of professional training, public education, and fundamental research. Seven major research areas have been selected by the Scientific and Educational Council as being "most worthy of investigation." They are: studies of the ways in which cells of the body are affected by antigens; studies of ways to prevent autibody formation so that no reactions occur when sensitizing antibodies meet the antigens for which they are specific; a study of histamine metabolism; further study of enzymes; basic research into the causes of autosensitization; advanced research in the collagen diseases; and studies of psychophysiologic factors in allergy. The Foundation plans to offer post-doctoral research fellowships to qualified physicians and scientists who make application. The number of fellowships will vary from year to year, but it is the Foundation's desire to set up eighteen or more projects in the next three years at a cost of about $350,000.

FUNGI AND BACTERIA IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XIX. Bacteria, Actinomycetes, and Yeasts: Atmospheric Studies including a Dust Storm

MARIE B. MORROW, Ph.D., F.A.C.A., Austin, Texas; GEORGE H. MEYER, M.A., Austin, Texas; L. O. DUTTON, M.D., F.A.C.A., El Paso, Texas, and HOMER E. PRINCE, M.D., F.A.C.A., Houston, Texas

SINCE the eighteenth century, when Michaeli studied air distribution of "spores," and Spallanzani argued the dissemination of "mold seeds," our knowledge of the biology of air has been advanced spectacularly. This is particularly true of this century and has come from various fields of investigation, phytopathology, agriculture, industry, meteorology, public health and medicine, and from the academic.

Aerial studies have been made in all parts of the world. Investigations have been extended beyond the local environment to include different kinds of upper air masses. These include terrestrial and marine air, tropical and polar air, and atmospheric dusts. All altitudes have been studied. The organisms have been collected variously by means of slides, plates, and impinging apparatus. Pollens, molds, bacteria, rusts, smuts, algae, and many other biologic objects have been identified.

A group project of The Association of Allergists for Mycological Investigations to study air-borne bacteria was an outgrowth of Dutton's[1] preliminary research on air-borne soil bacteria as a factor in respiratory allergic diseases. Interest stemmed from the fact that certain unexplained clinical respiratory symptoms, which developed during or following dust storms of the Southwest, could best be explained by bacteria incident to these storms. A pilot experiment was designed to determine a rough index of the number and general types of bacteria in the air at various locations in the United States, and to attempt to corroborate clinical evidence that certain skin reactions are attainable with crude bacterial antigens.

At Austin, Texas, it was proposed to study not only bacteria, but also actinomycetes, yeasts, and molds, and to make it a long-term project, seasonal in nature, and to include blowing dust. It seemed an opportunity to study the various factors involved in sampling air populations. One of these has to do with methods for trapping the organisms so as to get the maximum and most representative catch at any sampling. Another has to do with the media for the development of maximum numbers and types of

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From The Plant Research Institute, The University of Texas, in collaboration with The Association of Allergists for Mycological Investigations, Inc.
Presented at the scientific session of The Association of Allergists for Mycological Investigations, Chicago, Illinois, April 27, 1955.

TABLE I. BACTERIA, ACTINOMYCETES, AND YEASTS, FIRST AND SECOND SERIES

	8-15-53 Summer	11-13-53 Fall	1-30-54 Winter	2-20-54 Dust	5-1-54 Spring	t	9-28-54 Summer	11-2-54 Fall	12-7-54 Winter	3-1-55 Dust	t	T
°F	82	49	63	48	77		78	52	49	83		
%h	79	93	99	34	83		86	45	42	21		
WIND	SW 3	NE 3	SSE 5 fog	WSW 10 shift from NW	SSE 18		SSW 15	NNE 10 gusty to 23	S 4	NE 10 fog AM dust PM		
Bacteria												
Sporeforming bacteria total						∞						
Bacillaceae												
Bacillus subtilis	3	15		*	64	82	16	2	15	64	97	
Bacillus cereus		7		*	9	16	11		3	15	29	
Bacillus mycoides		1		*	3	4				1	1	
Bacillus globigii	2		2	*	21	25	3	6		2	11	
Bacillus pumilis			1	*	10	11	2	2		47	51	
Bacillus	15	14	8		11	48	1		7		8	
total	20	37	11	∞	118	186 ∞	33	10	25	129	197	383 ∞
Non-sporeforming bacteria total												
Pseudomonadaceae												
Xanthomonas		3	2			5						
Azotobacteriaceae												
Azotobacter	2	1	1		1	5						
Rhizobiaceae			1		3	4						
Micrococcaceae												
Micrococcus candicans	1		9			10						
Micrococcus luteus												
Micrococcus roseus	2	4	2		19	27	3	1	22	11	37	
Micrococcus cerasinus	1				3	4			1	5	6	
Micrococcus sulfureus	1					1						
Micrococcus	3	4	3		1	11	4	3	17	26	50	
Sarcina lutea	3		1		2	6						
Corynebacteriaceae												
Corynebacterium	13	4	4		26	47	15	9	81	57	162	
Achromobacteriaceae												
Flavobacterium	1	4	1		12	18	2	2	3	2	9	
Enterobacteriaceae												
Serratia		1			2	3						
Bacteriaceae	6	4	3		6	19	15	24	64	5	108	
Coccoid rods		1	2			3						
Undetermined rods	2		3			5	26				26	
total	35	26	32		75	168	65	39	188	106	398	566
Total	55	63	43	∞	193	354 ∞	98	49	213	235	595	949 ∞

* Counts of bacteria (ca. 1000) not included in numerical totals.
∞ Counts of bacteria more than 60 per plate

TABLE I. BACTERIA, ACTINOMYCETES, AND YEASTS, FIRST AND SECOND SERIES (Continued)

	8-15-53 Summer	11-13-53 Fall	1-30-54 Winter	2-20-54 Dust	5-1-54 Spring	t	9-28-54 Summer	11-2-54 Fall	12-7-54 Winter	3-1-55 Dust	t	T
°F	82	49	63	48	77		78	52	49	83		
%h	79	93	99	34	83		86	45	42	21		
WIND	SW 3	NE 3	SSE 5 fog	WSW 10 shift from NW	SSE 18		SSW 15	NNE 10 gusty to 23	S 4	NE 10 fog AM dust PM		
Actinomycetes												
Streptomyces												
gray spores		5	1	78	12	96	17	5	32	17	71	
pink spores	4		3		9	16	1	1	1		3	
S. rubrireticuli												
S. lavendulae												
blue spores	3					3						
S. viridochromogenes												
green spores									4		4	
S. griseus												
white spores		6	1		1	8		1		9	10	
undetermined		2				2						
Nocardia		2	2		1	5		1		2	3	
Total	7	15	7	78	23	130	18	8	37	28	91	221
Yeasts												
Rhodotorula			1		1	2				2	2	
Cryptococcus			7		6	13	1		3		4	
Sporobolomyces					1	1						
Ustilago					1	1						
Pullularia			2	76	7	85	1	6	2	6	15	
Total			10	76	16	102	2	6	5	8	21	123

the different organisms. It was also proposed to examine weather factors, as these might be correlated with the various microbial groups.

The allergist is concerned with those microörganisms which are disseminated by air. Whether they cause sensitization depends on many factors, concentration in the air, rate of deposition, their biochemistry in respect of allergens, and the predisposition of the patient to become sensitized. These aspects of aerobiology are summarized by Maunsell.[2] All air-borne spores and other particles settle sooner or later, depending on particle size as well as atmospheric conditions. After losing their initial speed, spores may drift for long distances, carried up and down by convection currents, but will fall at a constant speed known as "terminal velocity," depending on their size and density. Large spores like *Alternaria* and small, moist spores like *Pullularia,* occurring in balls, or *Hormodendrum* spores, falling in clumps, will be trapped fairly completely. Dry, small spores like *Penicillium,* will be trapped only in a small percentage if they travel as single units. When turbulence is strong, those particles may be kept aloft which would fall rapidly under calm conditions.

EXPERIMENTAL

The air sampling dates at Austin fall into two series. The first series includes dates selected so that each season is represented and, in addition, a date of blowing dust: summer (August 15, 1953), fall (November 13, 1953), winter (January 30, 1954), dust (February 20, 1954) and spring (May 1, 1954). The second series includes summer (September 28, 1954), fall (November 2, 1954), winter (December 7, 1954), and dust (March 1, 1955). A current spring date is lacking.

Gravity plates were selected for air sampling. Different kinds of impinging devices were tested, but none of these gave maximum numbers and kinds of organisms on comparison with plates exposed direct to the air. Membrane filters were also tested with the various impinging apparatus, in order to detect the organisms, and at the same time stain them in place for microscopic examination. The membrane filters were used both for collection of air by direct filtration through the filter disc (aerosols), and for filtration of air trapped in a collecting medium (hydrosols). The success of the plate method depends upon the selective media used, the replication of plates, and the temperature at which the plates are incubated.

Plain nutrient and Waksman's acid glucose media were used for all the sampling dates. For the last three dates, four additional media, which varied in composition and pH, phytone, wort, Czapek's, and corn meal, were introduced. The phytone medium varied from the Waksman's formula, only in phytone, a papaic digest of soya meal, being substituted for peptone. While plain nutrient (pH 6.8) is selective for bacteria and actinomycetes, and Waksman's (pH 5.8) for molds and yeasts, some kinds of each group develop on both media. Wort (pH 5.5) is particularly suitable for the isolation of molds by the plate method. Czapek's (pH 7.3) is recommended for the hyphomycetous fungi, where pigmentation is a factor in identification, and for bacteria and other fungi, where an inorganic source of nitrogen is indicated. Corn meal (pH 6.0) is recommended for yeasts and fungi, when it is desirable to force spores and other reproductive structures, and to restrict the growth of mycelium. More different organisms develop on phytone (pH 5.8), but growth is so profuse that overgrowth occurs.

In order to provide random sampling, replicate plates were exposed to different directions, North, East, South, and West. Windows of second story laboratories

were selected for sampling locations. At these windows, the window guard forms with the ledge a device so that the spores and other "biological fall-out" in the air can be trapped on exposed plates, both by sedimentation and by impaction. By exposing plates to the different directions, in addition to providing chance sampling, the catch at any one of these sites might be correlated with weather factors, as wind direction.

Duplicate plates of each medium were exposed for a period of fifteen minutes at the different sampling locations.

The exposed plates were incubated at 25° C (room temperature) and 37° C. While room temperature is conventional for molds and yeasts, and 37° C for bacteria and actinomycetes, some kinds of each group develop at one or the other temperature. Plates incubated at 37° C were removed to room temperature after forty-eight hours. Plates held at the elevated temperature, and then removed to room temperature, are referred to in the text as "37° C plates." The plates held continuously at room temperature are called "25° C plates."

The weather data for each sampling date was obtained from the United States Weather Bureau for 8:30 a.m., which was the time plates were exposed, except in the case of the last dust date which was 2:30 p.m. Air temperature, in degrees Fahrenheit (82, 49, 63, 48-dust, 77; 78, 52, 49, 83-dust), varied no more than 34° F from season to season. There was a difference of only 35° F between the lowest (48° F) and highest (83° F) readings, which were the respective dust dates.

Relative humidity, in percentages (79, 93, 99, 34-dust, 83; 86, 45, 42, 21-dust), showed variability from season to season. There was a difference of 65 per cent between the lowest and highest readings in each series, the low readings in each case being the dust dates, (34 per cent and 21 per cent). Low humidity was a feature in both dusts.

Wind direction and velocity, mph (SW 3, NE 3, SSE 5, WSW 10 dust, SSE 18; SSW 15, NNE 10, S 4, NE 10 dust), follow a more or less seasonal pattern for direction in the two series, with the exception of the dust dates. This is not as apparent in the wind speed. Differences between the lowest (3 mph) and highest (18 mph) speeds were not great. On the dust dates, the wind velocity was only 10 mph, but the wind was from opposite directions (WSW 10 and NE 10). On the first date, the wind had shifted during the blowing dust (from NNW). The dust had been in the air for several days. On the second date, the dust came up quickly, following fog the same morning. The blowing dust encountered at Austin is not a dust "storm," rather the dust seems to be pushed in without turbulence. The dust at Austin is not sand. The data with respect to temperature, humidity, and wind are being studied for correlation with the seasonal microbial groups.

RESULTS

The results of the experiment are summarized variously for the firs and second series of sampling dates. These include tables which show correlations between the organisms isolated and the different factors involved. At this time, we can point up certain facts which the results reveal, as they pertain to the numbers and kinds of organisms encountered, and to the methods employed. These are reported in this paper for bacteria, actinomycetes and yeasts. Molds are reported in a separate paper.

A diverse assortment of organisms is exhibited on the various media.

Colonies of sporeforming bacteria can be distinguished on the 37° C plates at the end of forty-eight hours. By the end of the incubation period, numbers of colonies are not noticeably different on the 25° C and 37° C

plates. Sporeforming bacteria appear on all of the carbohydrate media as well as plain nutrient. Colonies of non-sporeforming bacteria develop more slowly on the 25° C plates, but in greater numbers. Chromogenic bacteria usually do not appear on the 37° C plates until removed to room temperature. Non-sporeforming bacteria appear on all the carbohydrate media except wort. Apparently the saprophytic bacteria are not favored at 37° C.

Actinomycetes appear early on the plates, but are rarely distinguishable from bacteria until characteristic colony features develop. *Streptomyces* grows on carbohydrate media, but more different types develop on plain nutrient, especially the type with gray spores. *Streptomyces* on most media is favored at 37° C. *Nocardia* appears only on plain nutrient and at both 25° C and 37° C.

Yeasts usually appear after the third day, but distinguishing features develop later. The true yeasts seem to favor carbohydrate media, but appear on plain nutrient, and mostly at 25° C. The yeast growth-form, *Ustilago,* develops at 37° C. The yeast growth-form, *Pullularia,* appears only at 25° C, mostly on carbohydrate media.

We are not convinced that the catch at any one of the sampling locations can be correlated with wind direction or other weather factors. From the results so far, it would seem that the sampling locations in the different directions provide random and chance sampling.

For bacteria, totals on the first dust date to those on the second are in a ratio of about five to one, but consist almost entirely of spore-forming bacteria, about the same numbers at the different sampling locations. On the second dust date, the *Bacillaceae* make up about one-half of the total, the rest consisting mostly of *Micrococcaceae* and *Corynebacteriaceae.* The remainder of the catch is made up of *Achromobacteriaceae, Enterobacteriaceae,* and *Bacteriaceae.* Fewer different species of non-sporeforming bacteria are recovered from dust than in the routine seasonal samplings. In the routine seasonal sampling, the sporeforming bacteria can be expected to make up less than one-half of the total catch. All of the species of the sporeforming bacteria encountered in this study are represented in the dust catches. *Bacillus subtilis* and *B. pumilis* are the dominants from dust. *Bacillus subtilis, B. cereus,* and *B. globigii* are the dominants on the other dates. By its consistent high numbers in dust, and low numbers in the seasonal catches, *Bacillus pumilis* stands out as an indicator or a "marker" of the aseasonal weather conditions.

For actinomycetes, *Streptomyces* is consistent in the dust plates of both dates, as well as the routine seasonal plates, but numbers are higher in the dust. Counts are not very different at the four sampling locations. In the first dust, the gray type of *Streptomyces* predominates, in the second dust, gray and white types are represented. *Nocardia* is seen in the routine seasonal plates. It appears in the last dust plates. No correlation is apparent between occurrence and sampling locations.

The true yeasts, *Rhodotorula, Cryptococcus,* and *Sporobolomyces,* and the yeast growth-forms, *Ustilago,* and *Pullularia,* appear at one time or another in the routine seasonal samplings. No correlation is indicated with sampling locations. No true yeasts were recovered in the first dust. Only *Rhodotorula* appears in the second dust, but numbers are low. *Pullularia* was recovered on both dust dates. Numbers of *Pullularia* in the first dust exceed those in the second dust more than ten to one. Since *Pullularia* is thought to be disseminated by means of moist spore balls, it is conspicuous that a high *Pullularia* catch is obtained when the humidity is relatively low. For *Pullularia* this may be an indication of survival in the air under adverse atmospheric conditions. With respect to wind direction, the *Pullularia* catch apparently has no significance.

Numbers and kinds of bacteria, actinomycetes, and yeasts, correlated with the routine seasonal dates, and the dust dates, are shown in Table I, for the first and second series of sampling dates. Weather factors are included. All of the organisms recovered at the North, East, South, and West locations, on plain nutrient and Waksman's media, and incubated at 25° C and 37° C, for each date are listed.

The bacteria are placed in families, and in species where these have been determined. The following families are represented: *Pseudomonadaceae, Azotobacteriaceae, Rhizobiaceae, Micrococcaceae, Corynebacteriaceae, Achromobacteriaceae, Enterobacteriaceae, Bacteriaceae,* and *Bacillaceae.* Genera identified include *Xanthomonas, Azotobacter, Micrococcus, Sarcina, Corynebacterium, Flavobacterium, Serratia,* and *Bacillus.* Species in the *Micrococcaceae* follow the classification of Lehmann and Neumann: *Micrococcus candicans, M. luteus, M. roseus, M. cerasinus, M. sulfureus,* and *Sarcina lutea.* Species in the *Bacillaceae* follow Bergey: *Bacillus subtilis, B. cereus, B. mycoides, B. globigii,* and *B. pumilis.*

The actinomycetes are represented by *Streptomyces* and *Nocardia.* As presently accepted, they are classed in the *Actinomycetales* co-ordinate with the *Eubacteriales* in the *Schizomycetes.* The *Streptomyces* are separated into types on the basis of spore color: gray spores, pink spores, blue spores, green spores, and white spores, criteria used by Hesseltine.[3] The *Nocardia* are all pigmented types, coral and pasty, with mycelial margins. They are not designated for species. When actinomycetes are encountered in culture, they must be differentiated from yeasts and bacteria which may exhibit similar growth features. *Streptomyces* and *Nocardia* are apparently saprophytes of soil origin.

Yeasts and yeast growth-forms are reported as a group. Yeast growth-forms are known in all classes of the *Eumycetes.* The true yeasts are represented by *Rhodotorula, Cryptococcus,* and *Sporobolomyces,* the yeast growth-forms by *Ustilago* and *Pullularia.* Air borne pale yeasts are probably not spore-bearing yeasts, as *Saccharomyces* (brewer's and baker's yeasts). The air isolates noticeably fail to produce ascospores which identify *Saccharomyces.* Actually, the pale yeasts are mostly *Cryptococcus,*

a torula yeast, and can be recognized by the morphological feature of encapsulation. *Rhodotorula,* a pink torula, is recognized by the single morphologic feature of budding. These "buds" are called blastospores. *Sporobolomyces* has both buds and basidiospores. The latter are called ballistospores, and distinguish *Sporobolomyces* from the pink torulas.

Ustilago is the only smut isolated in this study. The grass and cereal smuts develop in artificial culture as yeast growth-forms.

Pullularia may be discussed with the other dark imperfect fungi, or with the yeasts and yeast growth-forms. When first encountered on plates, *Pullularia* and other yeast-like forms have growth features in common that are not distinguishing. In the early stages of growth, it is difficult to distinguish *Pullularia, Rhodotorula, Cryptococcus, Sporobolomyces, Nocardia,* and the cereal smuts, as *Ustilago* and *Sphacelotheca,* and certain bacteria and actinomycetes in their early stages. Changes in colony appearance, pigmentation, and micro-features occur, as growth continues. The pink *Pullularias* might be reported as pink yeasts, pigmented bacteria, or the pigmented *Nocardia,* if presumptive plate identifications are not verified. Both pink and dark *Pullularias* have been isolated in this study.

SUMMARY AND CONCLUSIONS

Bacteria were present in all of the seasonal and dust plates. Counts of the sporeforming bacteria were greater in the dust. Only a small number of different species was encountered, but they were found in both the seasonal and dust catches. This would seem to indicate that they can survive the weather conditions coincident with the dust. The seasonal catch is probably local, with respect to sources, whereas the dust catch must be, in part, other than local. The same species in both catches must be indicative of the dominance of all of these sporeforming bacteria in the air under different weather conditions.

Seasonal counts of the non-sporeforming bacteria were higher than those of the sporeforming bacteria. Although the counts were high on the second dust date, no non-sporeforming bacteria appeared on the first dust plates. The large number of different species in the seasonal catches of the first series, and the absence of these from the dust, suggests local sources, or inability to survive the dust conditions. Not all of the species in the first series were recovered in the second, but the same species appeared in both the seasonal and dust plates. Therefore, some of the non-sporeforming species survive dust conditions under some circumstances.

Actinomycetes were present in all of the seasonal and dust plates. Counts, although low in comparison to bacteria, were, for the most part, greater in the dust, and a reflection of *Streptomyces.* No trends were indicated for *Nocardia,* recovered seasonally, and from the second dust. The seasonal catches yielded more different types of *Streptomyces.* This would seem to indicate the inability of some types to survive the dust con-

ditions. Seasonal incidence is a reflection of local sources. Other sources may be a factor in the dust.

Yeasts and yeast growth-forms were not always present in the seasonal plates, but the same species found in dust were seen also in the seasonal plates. Numbers of the true yeasts were always low, but counts of *Cryptococcus* exceeded those of *Rhodotorula* and *Sporobolomyces*. Only *Rhodotorula* appeared in the dust, and only in the second series. The smut, *Ustilago*, was recovered only in the spring of the first series. Counts of *Pullularia* were high in the first dust, but relatively low in the seasonal plates and second dust. Survival of *Pullularia* was noticeable in the aseasonal dust conditions where the humidity was low. For the yeasts and yeast-like species, incidence is a reflection of their sources.

For the microorganisms recovered from atmospheric dust, the time interval during which the dust is aloft as well as the source and origin of the dust are suggested as factors in the survival of these organisms. Population studies in relation to weather conditions are being investigated further, particularly with respect to these factors.

ACKNOWLEDGMENT

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The University of Texas (Dr. Morrow)

Submitted September 14, 1955

AMERICAN ASSOCIATION OF IMMUNOLOGISTS

The American Association of Immunologists will hold its annual meeting in conjunction with the fortieth annual meeting of the Federation of American Societies for Experimental Biology at Atlantic City, New Jersey, April 16-20, 1956. Scientific sessions will be held at Convention Hall and Hotels Dennis, Ritz Carlton, and Marlborough-Blenheim, with AAI headquarters at Chalfonte-Haddon Hall. Registrations should be made with the 1956 FASEB Meeting Housing Bureau, 16 Central Pier, Atlantic City, New Jersey. The six constituent societies of the Federation will again have intersociety sessions in fields of overlapping interest.

ADJUNCTIVE PENICILLIN PROPHYLAXIS FOR BACTERIAL ALLERGY

A Preliminary Report

V. L. SZANTON, M.D., F.A.C.A.,
Ansonia, Connecticut

H. COHEN, M.D., and H. G. RAPAPORT, M.D., F.A.C.A.,
New York, New York

THIS preliminary report on the prophylaxis of bacterial allergy with repository penicillin in conjunction with hyposensitization therapy covers a discussion of seventeen cases with controls, and the findings are suggestive rather than conclusive.

It has been recognized for many years that infections of the respiratory tract, upper or lower, play a significant etiologic role in the causation of bronchial asthma noted in individuals of all ages and specifically children. There are difficulties however in establishing an absolute relationship between a bacterial infection and allergic symptoms. The principal difficulty lies in the failure of bacterial extracts or vaccines to produce the characteristic immediate whealing type of skin reactions; i.e., the skin reactions which have proven so useful in the corroborative diagnosis of allergic conditions such as hay fever or asthma due to pollens, heterologous sera, foods, et cetera. Thus, the only basis on which the diagnosis of specific bacterial sensitization in a patient can be made is the information obtained from a carefully detailed history and repeated clinical observations of the cause and effect on the allergic state. After a case has been adequately investigated allergically and all other causal factors eliminated, and then only from the clinical viewpoint, one can arrive at the diagnosis of bacterial allergy.[3]

The use of antibiotics orally and/or systemically, both from the therapeutic and prophylatic approach in infectious asthma, has been reported in the medical literature.[1,4] However, the utilization of a long-acting repository penicillin in individuals with asthma associated with infection has not been described.

This preliminary report suggests consideration of an adjunctive prophylactic approach to the problem of bacterial allergy in asthmatic children. The low incidence of allergic reactions to repository penicillin has been reported by Levin and Moss[2] in the treatment of infectious asthma in children. Stollerman and Rusoff[5] have reported a similar low incidence in children who had received prophylactic penicillin for rheumatic fever. The repository type of penicillin was administered intramuscularly.

From the Pediatric Allergy Clinic, Pediatric Service, Mount Sinai Hospital, New York.

Presented at the Eleventh Annual Congress of The American College of Allergists, Chicago, Illinois, April 29, 1955.

It was felt that this type of prophylactic therapy was worthy of trial in asthmatic children who had a clinical diagnosis of bacterial allergy.

CLINICAL MATERIAL

A group of seventeen patients, varying in age from four to sixteen years, was chosen, in all of whom a clinical diagnosis of bacterial asthma had been made. All were seen at weekly intervals in the Pediatric Allergy Out-Patient Clinic at Mount Sinai Hospital, New York, over a period of two years or more. Etiologic factors in each case included bacterial allergy in addition to other specific causative allergens which were suggested by routine skin testing and confirmed by the history and clinical trial.

A similar group of thirteen patients served as a control group. These patients were of the same clinical category of asthma, with etiology established as bacterial allergy as well as other allergies. The patients in both groups presented the usual clinical pattern of bacterial allergy, i.e., respiratory infection immediately or closely followed by attacks of asthma. Initially, both the treated and control groups were much larger; however, during the period of study some discontinued treatment while in other instances the followup data were inadequate and were discarded.

TREATMENT

Each patient in the group under treatment was given 1,200,000 units of N. N'dibenzylethylenediamine dipencillin (Benzathine),* a repository type of penicillin, intramuscularly, at four-week intervals. A commercially available preparation in a disposable syringe type of unit was used. The site of injection was the upper outer quadrant of the buttocks. This therapy was started in December, 1953, and continued for a period of five months up to and including April, 1954. In addition, these patients continued to receive such hyposensitization injections as they had been receiving previously for specific inhalants, pollen, et cetera. The control group received the usual weekly hyposensitization injections, but did not receive any repository penicillin. All of the patients were seen at weekly intervals and all were on perennial type of therapy.

RESULTS

Progress was evaluated separately within each group, i.e., by comparing the attack rate in 1953 with the attack rate in 1954 for each of the two groups, the "prophylactic penicillin" treated group and the control group. The results were then contrasted.

Incidence of asthmatic attacks and attacks of upper respiratory infection in both groups, from December, 1952, to December, 1953, the year prior to the penicillin therapy here presented, was rechecked and recorded.

*Bicillin® (Wyeth) provided for this study through the courtesy of Dr. E. F. Roberts of Wyeth, Inc.

During five months of the second year (December, 1953, through April, 1954) the patients in the treated group received, in addition to their usual therapy, the "prophylactic penicillin" therapy previously described, and

TABLE I. PENICILLIN TREATED CASES.
ATTACK INCIDENCE—DECEMBER TO NOVEMBER
(INCLUSIVE)

Case	Dec. 1952-53 Before Bicillin		Dec. 1953-54 During Bicillin		Results	
	AS	URI	AS	URI	AS	URI
J.A.	1	2	0	0	+	+
A.E.	2	2	3	0	−	+
J.G.	5	5	0	5	+	−
P.J.	7	1	6	2	+	−
C.G.	5	5	3	2	+	+
V.M.	2	4	1	2	+	−
E.M.	7	4	4	6	+	−
R.N.	6	1	2	0	+	+
A.P.	4	3	3	2	+	+
R.Q.	1	3	1	2	−	+
R.R.	0	6	1	1	−	+
G.S.	10	6	0	0	+	+
C.T.	4	2	2	2	+	−
L.S.	10	4	1	2	+	+
S.S.	8	6	1	2	+	+
P.D.	7	5	0	1	+	+
N.S.	8	7	2	3	+	+

Summary:
Improved asthma; improved URI: 9
Improved asthma; unimproved URI: 5
Unimproved asthma; improved URI: 3
Unimproved asthma; unimproved URI: 0
Legend:
AS—Attacks of Asthma
URI—Attacks of upper respiratory infection
+—Improved
−—Unimproved or no change

the two-year comparison of incidence of attacks within this group is described in Table I. This shows a decrease in asthma and respiratory infection attacks in nine patients, a decrease in asthma but no decrease in respiratory infection attacks in five patients, and no decrease in asthma but a decrease in respiratory infection attacks in three patients.

Contrasted with these figures are those made for the control group (Table II). This shows decrease in asthma and respiratory infection attacks in two patients, a decrease in asthma but no decrease in respiratory attacks in two patients, no decrease in asthma and a decrease in respiratory infection attacks in four patients, and no improvement in asthma or respiratory infection attacks in five patients.

A summary of results indicated that, of the seventeen patients comprising the treated group, nine were improved, as evidenced by decreased incidence of both asthmatic and respiratory attacks; five showed decreased incidence of asthmatic attacks only (Table III). In contrast, in the thirteen control cases, only two showed improvement evidenced by a decreased incidence of asthmatic attacks alone (Table III). This table indicates an appreciable improvement in the treated group when compared with the control group.

There were no allergic reactions to penicillin in the patients of the treated group.

TABLE II. CONTROL GROUP—(NO PENICILLIN). ATTACK INCIDENCE DECEMBER TO NOVEMBER (INCLUSIVE)

Case	Dec. 1952 to Nov. 1953		Dec. 1953 to Nov. 1954		Results	
	AS	URI	AS	URI	AS	URI
H.A.	0	0	0	0	−	−
C.J.	3	3	3	4	−	−
T.B.	3	3	1	1	+	+
J.B.	3	3	3	3	−	−
P.B.	2	2	5	2	−	−
J.C.	2	5	8	0	−	+
A.C.	1	6	2	0	−	+
G.B.	1	1	0	1	+	−
A.A.	3	0	0	0	+	−
D.B.	2	3	1	2	+	+
A.C.	2	3	2	1	−	+
D.A.	0	2	0	0	−	+
J.C.	0	1	2	0	−	−

Summary:
Improved asthma; improved URI: 2
Improved asthma; unimproved URI: 2
Unimproved asthma; improved URI: 4
Unimproved asthma; unimproved URI: 5

Legend:
AS—Attacks of Asthma
URI—Attacks of upper respiratory infection
+—Improved
−—Unimproved or no change

TABLE III. SUMMARY OF RESULTS

	Penicillin Treated	No- Penicillin Controls
Improved Asthma +URI	9	2
Improved Asthma +Unimproved URI	5	2
Unimproved Asthma +Improved URI	3	4
Unimproved Asthma +Unimproved URI	0	5
Total	17	13

Legend: URI—Upper respiratory infection

SUMMARY AND CONCLUSION

A group of seventeen asthmatic patients with the diagnosis of bacterial allergy as an etiology is presented, with the response to adjunctive prophylactic repository penicillin therapy. Over a period of one winter season, contrast is made with previous year without benefit of adjunctive long acting penicillin therapy. A control group of cases with similar clinical diagnosis is also presented.

Data indicate an improvement in the treated group, in contrast to the control group. Results are not conclusive because of the small number of patients treated and of the relatively short duration of this preliminary study, but they do suggest that further trial of this prophylaxis is indicated to establish definitive conclusions.

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259 Main Street (Dr. Szanton)

Submitted June 6, 1955

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare, has recently announced an expanded program of research in allergy and infectious diseases. This program will be administered by the National Microbiological Institute, which is being redesignated as the National Institute of Allergy and Infectious Diseases. The Institute will also support long-term basic studies in these fields through grants to research scientists in the universities and medical schools of the country. According to Dr. Scheele, "The renaming of the Institute reflects the importance of the new research program on allergies and the close relationship of such research with the study of infectious diseases. Investigations of allergy are closely allied to the science of immunology, which is also fundamental to investigation of the infectious and parasitic diseases."

A separate national advisory council on allergy and infectious diseases is being established to make recommendations to the Surgeon General regarding the money granted and the training activities. A release from the Public Health Service states that "Allergy has received relatively little attention in the past from scientific investigators. Research knowledge offers little beyond description of the types and symptoms of the allergic conditions. Very little is known about the underlying mechanisms of the allergic response."

REPEATED ANAPHYLACTIC REACTIONS IN A PATIENT HIGHLY SENSITIZED TO PENICILLIN

A Case Report

K. J. BIERLEIN, M.D.
Pittsburg, Kansas

SEVERE anaphylactic shock precipitated by injected penicillin is becoming increasingly common. Reports of these frequently fatal allergic reactions are finding their way into the literature at an alarming rate and there is reason to believe that there are many more cases that are not published or reported as such. In spite of the fact that penicillin is generally known to be the most potentially dangerous of all the drugs used at the present time, it is still being produced at the rate of more than four hundred tons per year.

Kern and Wimberly[7] have shown that penicillin, for the past few years, has headed the list of all drugs in its frequency of production of sensitivities and far surpasses the serums in production of anaphylactic reaction. Brown[2] was one of the first to call attention to the specific dangers of this antibiotic as early as 1948 and has been most active in repeating the warnings for these past several years, and his efforts along with the efforts of others have likely aided a great deal in accomplishing the fact that the very same magazines which were extolling the virtues of penicillin a very few years ago are now warning the public of the dangers in the use of the drug.

This case report will also show not only some of the extreme dangers of use of the drug in sensitized individuals but also that the use of the ordinary method of determining penicillin sensitivity by skin testing may produce fatal anaphylactic shock in highly allergic patients. The curious fact that some individuals are reported to show sensitivity to the drug when no history of previous use of it can be elicited has been explained partially, at least, by the very interesting studies of Coleman and Siegel,[4] who have shown that syringes that have been previously used for administration of penicillin and then used for injecting other materials may still contain sufficient of the antibiotic to produce sensitization or produce an allergic reaction in an already sensitized patient. Bowen[1] has suggested that cow's milk is likely to contain enough penicillin to produce sensitization or reaction in milk drinkers. It is supposedly illegal for a pharmacist to dispense the drug without prescription from a physician, but it is likely that large quantities find their way to the public through this channel. It is fortunate indeed that oral preparations seem to be less likely to produce fatal anaphylaxis or a great many deaths might be attributed to illegal or irregular drug dispensing; however, this avenue may be responsible for some of the many unexplained sensitivities. Ordinary methods of

Dr. Bierlein is an Associate Fellow of The American College of Allergists.

syringe sterilization have been shown to be ineffective in destroying the antigenic power of the antibiotics, and it is doubtful the new high pressure method of sterilization designed to prevent spread of hepatitis is sufficient to deter this hypersensitizing faculty. It will be shown that the nationwide administration of Salk vaccine may also be expected to produce some of these allergic phenomena, especially when the vaccine becomes available to older age groups.

CASE REPORT

K.P., a white woman, aged fifty-five, a nurse in a physician's office, was first seen by us on March 25, 1955. Her chief complaint was marked allergic rhinitis and conjunctivitis beginning each Monday A.M., shortly after entering her place of employment and continuing through Friday. She was quite comfortable Saturday and Sunday, which were the only days she was away from the physician's office. Moderate wheezing accompanied her symptoms on some occasions. Symptoms first appeared early in January, 1955, after an attack of upper respiratory infection. She noticed her symptoms became exacerbated whenever she removed syringes from the sterilizer, so she began working in the reception room only and was able to continue work without as much discomfort.

Her allergic history was negative until four years ago when she lost about five weeks' work from a severe exfoliative dermatitis which was attributed to a "Cold Wave" she had previously received from a beauty salon. She was given ACTH every six hours for about five days and then an occasional dose for the next six weeks. It was about six months before the dermatitis completely subsided. She became symptom-free for the next one-and-one-half years when a bout of urticaria followed ingestion of a rather large quantity of cashew nuts. She was given an injection of 40 units of ACTH and immediately went into severe anaphylactic shock requiring adrenalin, aminophylline and other heroic measures. She was able to return to work in about three days but did not completely recover for a week. She believes some cortisone may have been used somewhere in her treatment, because shortly after this episode an oculist prescribed some cortisone drops which caused sneezing and produced an injected, swollen and itching eye.

In November, 1953, she received an intramuscular dose of 300,000 units of procaine penicillin and noticed a large hive over the injected area of the buttocks which lasted a few hours. During the next year or so she took a few doses of oral penicillin with no trouble. In January, 1955, she took a 200,000 unit tablet of long-acting penicillin and in about one-half hour her eyes became red and edematous, the palms of her hands and soles of her feet became painfully swollen, accompanied by much itching and an exacerbation of her upper respiratory symptoms (she had taken the penicillin as treatment for a common cold). She took some Phenergan® and codeine for relief of symptoms, and again broke out in urticaria for a few hours. Following these events, severe nasal symptoms accompanied by itching eyes appeared daily. She then took two weeks' vacation and became symptom-free except for an attack of sneezing and coughing when she mended a uniform which had not yet been laundered. When she returned to work, her symptoms returned with more intensity and became more severe during the elm-pollinating season.

We first saw her on March 20, 1955, at the request of her employer, who asked us to try to control her symptoms enough to allow her to continue to work. Her eyes were quite reddened and she was wearing dark glasses. Her nose was completely blocked and her symptoms became worse when she entered our treatment room where we were sterilizing syringes. Scratch tests were made on the common foods, inhalants, pollens, et cetera, and she reacted to elm, oak, cottonwood and house

dust and showed mild reactions to the weeds and grasses. She showed no reaction to the molds or fungi including the penicillium group. Since we were quite sure most of the symptoms were from penicillin, we decided to attempt to measure the degree of sensitivity by skin testing with serial dilutions of penicillin.[10] New bottles, stoppers, syringes and needles were autoclaved to prevent drug contamination, and a pure normal saline solution was used as a diluent. From a regular treatment bottle of aqueous crystalline procaine penicillin G containing 300,000 units per cc nine dilutions of 1:10 were made so that the ninth bottle represented a one to one billion dilution of the original. Of the ninth dilution .01 cc was given intradermally, this test dose containing .000003 units of penicillin. No scratch tests were made. Within two minutes the patient complained of feeling very faint and shaky and asked if she could lie down, so we carried her to a bed and immediately placed a tourniquet above the injection site. By this time her respirations were becoming rapid, wheezing and labored, her pulse was imperceptible and, except for a large, white, stellate area on the injection site, her body was red, and her lips and eyelids very swollen. Adrenalin was injected into the tested area and also into the arm. She did not completely lose consciousness on this occasion and stated she felt as if she were about to die. She became moderately cyanotic, but began to improve before oxygen therapy could be instituted. About two hours later she got up from her bed and returned to work.

Her nasal and eye symptoms continued as before and gradually became worse. She responded poorly to antihistamines so that on June 12, 1955 she returned and asked us to make another attempt to give her relief, so it was decided to make an extract of the dust from her employer's office. Blood was taken from the patient and the serum was diluted 1-1 with normal saline and .1 cc injected intradermally in several sites on a passive transfer subject. The dust extract was then diluted 1-5 serially, so that the second dilution represented a 1:25 mixture, the third a 1:125, the fourth a 1:625 et cetera. The highest dilution producing whealing reaction by intradermal testing in both the passive transfer subject and the patient was found to be 1:625. One-tenth cc of the 1:625 dilution was then prepared and, as an additional precaution, 10 mg. of a solution of Chlor-Trimeton® was added. This was then given to the patient hypodermically as the initial dose. Within two minutes she complained of extreme restlessness and asked to be allowed to lie down, after which she went immediately into severe shock, her pulse became imperceptible, heart tones could not be heard because of rather noisy respiration, but no true asthma appeared. She became unconscious but had no convulsions; there was no erythema nor urticaria, and she was very pale. After about fifteen minutes of heroic measures she regained consciousness, and her heart tones could be heard and counted at about 160 per minute with frequent extrasystoles. Warm blankets were applied to combat chill, and about one-and-one-half hours later she felt well enough to be taken home.

It was found that we had procured the Chlor-Trimeton from a rubber-stoppered vial which had previously had several doses removed from it and it was quite likely that it had been contaminated with penicillin, as it is our practice to include some of this antihistamine in most doses of parenteral antibiotics. In our immunologic studies we got a whealing reaction from this bottle of Chlor-Trimeton on passive transfer and, since we had never used the drug previously, we did not feel that she had become sensitized to it. Family history of the patient discloses that her mother, brother, and maternal grandfather all had allergic asthma. A sister has hay fever and another sister is sensitive to liver extract and an injectable estrogenic substance. We advised the patient to find different employment, but she is continuing to work as a receptionist and is having allergic symptoms five days a week.

IMMUNOLOGIC STUDIES

Passive transfer was done on several subjects using the patient's serum diluted 1:1 with normal saline. One-tenth cc was injected intradermally on several sites, and three days later the passive transfer areas were intradermally injected with .01 cc of each of several of the high dilution mixtures of penicillin which had been used previously in producing the shock reaction in the patient. Three-thousandths unit of penicillin was the minimal amount which would produce whealing reaction, and .03 unit was enough to produce a large wheal plus a flaring reaction to the other passively sensitized sites. This dose also produced an attack of sneezing in one passive transfer subject. Procaine failed to show a reaction and no whealing was produced with a fresh vial of Chlor-Trimeton. Whealing reaction was produced with .01 unit of aqueous ACTH of the same brand she had previously used. Cortisone was not tested. Milk was removed from her diet for four days and given to her on the fifth day, and as there was no noticeable change, it was assumed that the amount of penicillin found in the milk was not enough to produce symptoms when taken orally. On September 1, 1955 passive transfer studies were made using some of the serum taken from the patient in June, 1955. One of the same subjects used previously was used as transfer site, and it was found that distinct whealing reaction was produced with Salk vaccine diluted 1:25. The Salk vaccine literature stated that it contained "not over 100 units of penicillin per cc." It is possible that the patient's serum had lost some of its antigenic activity in two months, hence, the reaction to such a low dilution; or the vaccine may have contained much less than 100 units of penicillin per cc. A fresh supply of the patient's serum was not available at this time.

DISCUSSION

Collins-Williams and Vincent[5] in their review of anaphylactic deaths due to penicillin noted that severe sensitivity reactions were rare in children, and it was observed that one of their group of fatal accidents was precipitated by oral dosage. Halpin,[6] in his recent review of allergy, reported numerous fatalities and systemic reactions, but in this series there were no reports of anaphylactic reaction to oral penicillin. Madalin[8] noted that a patient had a severe reaction to a penicillin lozenge about two minutes after placing the medication in her mouth. Carter and Cope,[3] describe a milder shock reaction following use of a penicillin ophthalmic ointment and, since absorption is rather rapid from mucous membranes, that may explain the systemic reaction. These observations do not necessarily prove that oral administration of the medication is a safe procedure, but they do suggest that the comparative safety from severe reaction noted in the use of the newer antibiotics may be due to the fact that they are given orally and that most of the preparations utilized for systemic use are not as commonly prescribed in ointments, lozenges, and other local uses as is penicillin. Matheson and Elegant[9] state they were able to find only one report of anaphylactic death in a child from penicillin but they had knowledge of two unrecorded deaths. Of a group of 391 skin-tested patients, 353 (90 per cent) had had previous contact with penicillin, but only one child showed a positive whealing reaction; but in another group which had been hospitalized because of acute systemic reaction to penicillin, five of the total

of six children showed distinctly positive skin reactions. Passive transfer tests also demonstrated circulating antibodies in this series. This same report shows the dangers of using average concentration of penicillin for making scratch tests, as one child exhibited severe constitutional reaction following the use of one drop of solution of 5,000 units of penicillin per milliliter as a test dose. It should then be expected that reports should currently be finding their way into the literature describing anaphylactoid reactions following administration of Salk vaccine, especially when it is produced in large enough quantities to become available to the older children and adult groups. The concentration of the drug in the Salk vaccine is low enough so it is unlikely that scratch tests using undiluted vaccine, or intradermal tests using some dilution, will produce dangerous reaction, and that the immediate reactions may be prevented by doing routine skin testing before administration. This procedure, however, will not predict the delayed serum-sickness type of reaction. It is hoped that it will soon become unnecessary to use penicillin in the preparation of poliomyelitis vaccine.

SUMMARY AND CONCLUSIONS

1. A case of multiple drug hypersensitivity is described and the dangers of using ordinary concentrations of a drug in skin-testing a highly allergic patient are demonstrated.

2. As long as penicillin is being used in preparation of vaccines, there will always be a danger in employing these preparations without proper investigation to determine possible hypersensitivity to the drug.

3. Ridiculously small amounts of penicillin may produce a fatal or near-fatal constitutional reaction in highly sensitive patients, and great care should be practiced to prevent contamination of syringes and needles used to administer parenteral therapy to these patients.

4. It would seem that any attempt at hyposensitization of such a highly sensitive patient would be extremely dangerous and should not be attempted by employing injection therapy. No reports of attempts by use of gradually increasing oral dosage has been seen by us. Possibly this avenue of approach may have some merit.

5. As long as poliomyelitis vaccine contains penicillin it may produce anaphylactic shock or allergic reaction in those individuals sensitized to penicillin.

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902 North Broadway

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AMERICAN ACADEMY OF ALLERGY HOLDS TWELFTH ANNUAL MEETING

The American Academy of Allergy held its twelfth annual meeting at the Chase Hotel in St. Louis, Missouri, February 6-8, 1956, preceded by a two-day pre-convention scientific assembly consisting chiefly of panel discussions. A very large and enthusiastic group attended these sessions. Under the auspices of Ciba Pharmaceutical Products, Inc., addresses were presented by five outstanding speakers on various subjects: Carl V. Moore, M.D., Busch Professor of Medicine, Washington University School of Medicine, St. Louis, spoke on "Immunohematology"; Sidney Raffel, M.D., Professor of Bacteriology, Stanford University, discussed "Bacterial Hypersensitivity"; Irvin Kerlan, M.D., Associate Medical Director, Food and Drug Administration, Washington, D. C., presented "Foods, Drugs, Cosmetics and the Allergist"; Herman N. Eisen, M.D., Professor of Medicine (Dermatology), Washington University School of Medicine, St. Louis, spoke on "Some Mechanisms Involved in Allergic Contact Dermatitis"; and Charles A. Janeway, M.D., Thomas Morgan Rotch Professor of Pediatrics, Harvard University Medical School, Boston, Massachusetts, discussed "The Gamma Globulins."

Preceding the President's Luncheon, Dr. Lawrence J. Halpin, President of The American College of Allergists, gave an address. Eight scientific and forty-four commercial exhibits were presented at the meeting.

The 1957 annual meeting of the Academy will be held February 4-6 at the Statler Hotel, Los Angeles; the 1958 meeting, February 3-5, at the Bellevue-Stratford in Philadelphia; and the 1959 meeting, February 9-11, at the Morrison Hotel, Chicago.

SKIN ERUPTIONS FOLLOWING THE USE OF DIAMOX

MAXWELL SPRING, M.D.
Bronx, New York

DIAMOX® (Acetazoleamide) is a nonmercurial oral diuretic. Although a sulfonamide derivative, its structure and pharmacologic activity are totally different from those of bacteriostatic sulfonamides, and drug sensitivity reactions to it appeared to be unlikely.

Maren and Wadsworth[2] found it to be a substance of low toxicity in the animal; in man, in spite of widespread use, there have been few reports of toxicity following its use. Schwimmer et al[4] reported an instance of a febrile reaction resulting from this diuretic, and Breinin and Gortz[1] in a study of its effects in thirty-six patients with glaucoma, mentioned that two of their patients manifested toxic skin eruptions. One was a forty-nine-year-old male who developed an erythema of the extremities after ingestion of 3.5 gm of the drug over a period of five days; the other, a thirty-six-year-old male, exhibited facial edema, hives, and erythema of the extremities six weeks after the initial ingestion of the drug. The latter took 500 mg the first day and 700 mg daily thereafter. In both patients toxic signs cleared a few days after the medication was discontinued. Pearson et al[3] reported agranulocytosis following acetazoleamide therapy. Their patient was on 250 mg of this drug daily, but took it irregularly over a period of three months.

I wish to report two patients, one of whom developed erythema multiforme bullosum and the other a papular eruption following the use of Diamox.

CASE REPORTS

Case 1.—E.S., a fifty-year-old white woman, hypertensive, in cardiac failure, was first seen by me at her home early in November, 1953. For the previous thirteen months she had received mercurials by injection one to two times weekly. On examination she was found to be orthopneic, dyspneic, and cyanotic. There was nodal tachycardia and râles at the bases of both lungs. The liver was three fingerbreadths below the bases of both lungs. There was two plus pre-tibial edema On further questioning, it was discovered that she had been inadequately digitalized, and Digoxin® and Quinidine were prescribed. Her cardiac failure diminished markedly on this regime; thereafter, Mercuhydrin® intramuscularly was given as needed. On November 17 she was placed on Neohydrin®, one tablet three times daily, and the Quinidine was discontinued on December 8. On January 4, 1954, she was given 2 cc of Mercuhydrin intramuscularly. On this date Neohydrin was discontinued, and Diamox, one and one-half tablets (250 mg per table) daily, was substituted, but there was no improvement with this therapy.

After one week on Diamox therapy, an itchy, papular eruption developed on the

Dr. Spring is clinical instructor in medicine, New York Medical College, associate visiting physician, New York City Hospital, associate in radioisotope therapy and adjunct physician, The Bronx Hospital.

arms and legs. The patient herself discontinued the drug and returned to Neohydrin. An antipruritic (Caladryl®) was prescribed without avail. When seen the following week, January 28, the rash was worse but was still confined to the arms and legs. Pyribenzamine®, 50 mg three times a day, was prescribed and the Neohydrin was discontinued. By the next week the rash had become more extensive and urticarial in nature. Acthar Gel®, 2 cc (80 units) daily, intramuscularly, for three days, followed by hydrocortisone, 25 mg twice a day for several days, brought about a moderate diminution in the lesions and itching. On February 11, one cc of My-B-Den®* was given intramuscularly. About one hour after the injection the urticaria worsened. The cause of the eruption was still undetermined by February 2; therefore, all medication except Gitaligin®, a cardiac glycoside, was discontinued.

On February 21 Mercuhydrin, 2 cc intramuscularly, was given with no apparent effect on the skin eruption, which was now generalized except for the face, erythematous and vesicular. A dermatologist saw this patient in consultation on February 23. He thought she had erythema multiforme bullosum secondary to mercury, though Diamox could not be eliminated as a causative agent. He suggested the discontinuation of all medication except Gitaligin and the use of Acthar Gel 80 units daily, intramuscularly, plus hydrocortisone daily in decreasing doses starting with 60 mg daily for the following five days, and this program was undertaken.

By March 3 the rash had improved a great deal but her congestive failure was worse. She had 4 plus edema of the legs and the dyspnea had increased. Since mercury was thought to be the cause of her eruption, Diamox was reinstituted. During the morning of March 4, the patient took one-half tablet (125 mg) of Diamox. One half hour later itching started. At noon she took another half tablet, and one hour later urticarial wheals started to appear on her body. At 6 p.m. she took another one-half tablet, following which the urticarial wheals increased in number and became generalized and the itching became severe. That evening epinephrine hydrochloride in oil, 1 cc intramuscularly, was given, which gave some relief. The diuretic was discontinued, and Acthar Gel, intramuscularly, and hydrocortisone, orally, were restarted on March 6. By the next day the itching was gone and the acute lesions had disappeared. Mercuhydrin, 2 cc, was given without any flare-up of the skin eruption. Neohydrin was reinstituted on March 12. By April 3 the skin eruption was entirely gone, but the skin had a brownish pigmentation on the sites of the rash, which disappeared by May 1. Until her death on March 17, 1955, she had remained on Neohydrin orally and Mercuhydrin, intramuscularly as needed, without any recurrence of the eruption.

Comment.—There was no history of the ingestion of a sulfonamide. The initial skin eruption occurred one week after the institution of Diamox therapy. The drug was discontinued and the rash improved. Six weeks later the patient took one-and-one-half tablets (375 mg) of Diamox with a severe generalized recurrence of the skin eruption in the form of urticaria. This responded to steroid therapy and had entirely disappeared within a month.

Case 2.—L.B., a thirty-two-year-old white man, in congestive failure since 1953 due to coronary sclerosis, had been on Thiomerin® parenterally and then on Neohydrin orally plus Thiomerin for about a year. Neohydrin caused a severe diarrhea and had to be discontinued. On December 12, 1953 he was placed on Diamox, one-and-one-half tablets daily. After one week a non-itchy, papular eruption appeared on his arms and legs. The drug was discontinued and the rash disappeared. His cardiac failure then became refractory to treatment, and he required almost daily injections of Mercuhydrin. About two months after Diamox had first been given, he was

*My-B-Den contains in each cc adenosine 5-Monophosphate as the Sodium Salt 100 mg; gelatin 100 mg; dextrose 80 mg; phenol 5 mg as a preservative.

hospitalized for therapy for his cardiac failure. During his hospitalization Diamox was again instituted, and after a few days a papular eruption again appeared, this time on the chest, face, and neck. Since the Diamox seemed to help control his cardiac failure without the use of mercurials and the rash was not itchy nor extensive, the Diamox was continued. After a few days the rash disappeared spontaneously and there was no other toxic effect on the body from this drug.

Comment.—A mild, papular eruption developed after the first course of Diamox therapy. A few weeks later, on reinstitution of the drug, the rash appeared again, but in different areas of the body and more extensively. This therapy was continued, however, because the eruption was mild and the drug was controlling his failure. The rash disappeared spontaneously within a few days.

DISCUSSION

Any drug is capable of producing a hypersensitivity reaction in a susceptible individual. An occurrence of this kind is particularly likely when the drug in question is chemically related to or derived from those which are known to produce allergic manifestations. Thus, it is not surprising that Diamox, a sulfone derivative, can produce allergic manifestations.

The amount of drug ingested is one of the factors in the production of hypersensitivity. I have seen as little as one tablet (0.5 gm) of sulfathiazole produce a hypersensitivity reaction in a patient. In the case of Diamox, few reactions have been reported in the literature. Schwimmer et al[4] had a patient who developed a febrile reaction after ingesting one gm of the drug, and the reaction was reproduced by half a tablet (125 mg). In both my patients, two to two and one-half gm of the drug sufficed to produce the allergic skin eruptions, and one-half tablet resulted in a recurrence in both of the patients.

Depending upon the type of reaction, continuation of a drug which causes an allergic reaction may on occasion cause a disappearance of the allergic reaction. This is thought to be due to the development of drug tolerance by some unknown mechanism. This happened in the second patient.

CONCLUSION

Erythema multiforme bullosum and a papular eruption, respectively, followed the ingestion of about two to two-and-one-half gm of Diamox. The skin eruptions were reproduced after the reinstitution of small quantities of the drug. In one patient the eruption cleared after appropriate steroid therapy and in the other spontaneously in spite of continued medication.

REFERENCES

1. Breinin, G. M., and Gortz, H.: Carbonic anhydrase inhibitor acetazoleamide (Diamox). Arch. Ophth., 52:333-348 (Sept.) 1954.
2. Maren, T. H., and Wadsworth, B. C.: The pharmacology of Diamox, a new carbonic acid inhibitor. Bull. Johns Hopkins Hosp., 95:199-243 (Nov.) 1954.
3. Pearson, J. R., et at: Agranulocytosis following Diamox therapy. J.A.M.A., 157:339-341 (Jan. 22), 1955.
4. Schwimmer, J., et al: Febrile reaction to acetazoleamide (Diamox). New York State J. Med., 54:692-693 (March 1) 1954.

800 Grand Concourse
Bronx 51, New York

Submitted July 20, 1955

TOPICAL USE OF PREDNISOLONE IN NASAL ALLERGY

Report of a Controlled Study

JACK R. ANDERSON, M.D., and HENRY D. OGDEN, M.D., F.A.C.A.
New Orleans, Louisiana

THE topical use of cortisone and hydrocortisone intranasally has been studied. One of the advantages of this mode of administration is that, to our knowledge, no undesirable systemic effects have been reported.

Recently, a new analogue of hydrocortisone, known as prednisolone, has been developed. Inasmuch as it is said to be several times more potent than hydrocortisone, therapeutically speaking, it seemed desirable to determine its efficacy as a topical medication in the treatment of nasal allergy. As far as we know, similar studies with this preparation have not as yet been reported.

METHOD OF STUDY

This was a blind-placebo, controlled investigation and we were unaware of the contents of the three preparations until the completion of the study. Thirty patients with nasal allergy were selected from those attending the Allergy Clinic of the New Orleans Eye, Ear, Nose and Throat Hospital. Aside from the physical manifestations of nasal allergy, all had a positive family history, positive nasal eosinophilia, confirmatory skin tests, and a positive childhood history of allergy.

Three separate solutions were used; these were labeled A, C, and D, and were provided in the now familiar plastic spray bottles. At the conclusion of the study, the manufacturer revealed that Preparation A was the placebo, Preparation C contained 0.5 mg prednisolone per cc (a 0.05 per cent solution), and Preparation D contained 1 mg of the steroid per cc (a 0.1 per cent solution).* Each patient received each preparation for a period of one week. Between each treatment period, a rest interval of one week was inserted in order to avoid any carry-over effect from the previous preparation. Prior to dispensing each preparation, the results of a nasal and cytologic examination were recorded; at the end of the week these were repeated and the results compared. The same physician (J.R.A.) interviewed and examined the patients throughout the study in order to obviate conflicting objective interpretations.

All patients were instructed to use the preparation in the same way.

Dr. Anderson is Chief of Otolaryngology, Independent Service, Charity Hospital, and the Allergy Clinic of the Eye, Ear, Nose and Throat Hospital, New Orleans, Louisiana.

Dr. Ogden is Clinical Assistant Professor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana.

*Kindly supplied by the Upjohn Company, Kalamazoo, Michigan, as Delta-Cortef Acetate.®

They were instructed to give one squeeze of the bottle into each nostril every half hour while awake, for the first forty-eight hours; after this period they were told to reduce the dosage to one spray in each nostril four times daily.

Several other points in connection with the study were noteworthy. The patients were told that they were receiving different medications and could, therefore, expect different results with each. Secondly, different patients were on different solutions at the same time; this was done to eliminate the possibility of pollen or weather factors' influencing the results. However, the atmospheric pollen sampling in the city of New Orleans during the period covered by the study showed little variation.

RESULTS

None of the patients who received Solution A (the placebo) showed any clearcut subjective or objective improvement, when compared to the other two solutions. All patients reported varying degrees of subjective improvement after using Solutions C and D.

Twenty-four patients stated that they obtained more subjective improvement after using C than after using D; this was confirmed by examination of the nose. Most of these individuals were people whose nasal allergy was not accompanied by a great deal of metaplastic change in the nasal mucosa Six of the patients reported greater subjective improvement with Solution D than with Solution C; this was also confirmed by examination of the nose. The nasal allergy in these patients was farther advanced, therefore the mucosa showed more metaplastic changes, or they had been submitted to previous surgery which interfered with normal nasal physiology. Thus, it would appear that we can expect only a certain amount of improvement with the hormone whether in 0.1 per cent or 0.05 per cent solution. The 0.05 per cent solution is sufficient in the less advanced cases, while 0.1 per cent is necessary in the more advanced cases. It should be emphasized that all patients were helped. Five patients had polypoid degeneration of the mucosa, and there was no visible decrease in the size of the polyps following therapy.

At the end of one week's treatment with both Preparations C and D, there was a decreased amount of mucous secretion and a definite lessening in the percentage of eosinophilia.

DISCUSSION

These results were so definite that it was felt there was no need for statistical evaluation. Several points, however, are worthy of note in connection with this study.

Though the number of patients included is small, the requirements for inclusion of a case were rigid. In our opinion, some of the equivocal results obtained in the past with topical corticosteroid therapy in the nose

were due, in part, at least, to the inclusion of some patients in the studies whose nasal conditions resemble allergy. It is sometimes difficult even for experienced otolaryngologists or allergists, well versed in the differential diagnosis of nasal allergy, to make a definite diagnosis. Inclusion of such cases that mimic allergy will, of course, prejudice the results obtained.

It will be noted that frequent administration was used during the first forty-eight hours of treatment. This was done because it is well known that, in order for any such medication to be effective, a high initial tissue saturation is desirable; this is true whether the steroids be used orally or topically. We feel that this is another explanation for some of the poor results obtained previously with topical hydrocortisone therapy when used intranasally.

No visible changes were observed in nasal polyps during treatment, although there have been occasional reports in the literature to the effect that nasal polyps disappear during steroid therapy. The yardstick for measuring such reports, it seems to us, is the amount of metaplastic and submucosal fibrotic changes which have occurred in these structures. It is unrealistic to expect well-formed fibrotic tissue to be "dissolved" by hydrocortisone, or any other type of therapy currently available after irreversible changes have occurred; however, resolution would be no more surprising than it is under any other type of satisfactory allergy control. Another fact to be considered is the short duration of treatment used in this study.

SUMMARY

1. A blind-placebo, controlled study revealed that prednisolone is a rapidly acting and highly effective medication for topical use in the treatment of nasal allergy.

2. It is stressed that careful selection of cases and initial saturation of the nasal tissues is necessary in order to obtain good results with this or any other, type of topical steroid therapy in the nose.

301 Baronne Bldg. (Dr. Anderson)
Pere Marquette Bldg. (Dr. Ogden)

Submitted August 23, 1955

AILANTHUS GLANDULOSA POLLEN AS A CAUSE OF HAY FEVER

J. TAS

Jerusalem, Israel

SENSITIVITY to the "tree of heaven" is not frequently seen. Urbach (1949) claims to have seen one case only. Blumstein (1943) published reports of two cases.

During this spring four cases were seen in Jerusalem. Since the number of hay fever patients in our department is small, it is possible that the Ailanthus plays a role of some importance in the Jerusalem area, and the pollen should be used for routine testing.

The tree has multiplied very much in the last few decades. In his first report on hay fever in Palestine (1941), Gutmann did not mention the Ailanthus, but in his second report (1950) he states that the tree grows rapidly and has become "very common here in recent years."

The pollen is insect- and wind-borne, and it was found in a pollen survey during the months of April and May in 1953.

CASE REPORTS

Case 1.—A housewife, aged forty-seven, was referred to the skin clinic with the history that she had suffered for four years from hay fever during the blossoming period of a certain tree, which grows very close to her window. When she moved temporarily to another part of Jerusalem the symptoms virtually disappeared, but recurred when she returned to her own flat.

A scratch test with the pollen elicited a 4+ reaction.

Case 2.—A twenty-four-year-old female office worker reported to the clinic because of rhinitis and severe blepharo-conjunctivitis, which coincided with the blossoming period of the "tree of heaven" which grows in abundance in the neighborhood of her home as well as of her office.

Scratch test with the pollen elicited a 4+ reaction.

Case 3.—A thirty-three-year-old house painter suffered four years from hay fever during the blossoming period. Skin tests with grass pollen showed 4+. After the blossoming period (middle of May) he was well until this year, when his symptoms continued after the grass pollination season. Skin tests with Ailanthus pollen showed 4+. He recovered after the end of the Ailanthus season.

Case 4.—A forty-three-year-old nurse has suffered two years from hay fever during the months of May and early June. Testing with Ailanthus pollen caused a constitutional reaction.

From the Allergy Laboratory, Dermatological Department, Hebrew University-Hadassah Medical School.

In all the patients, testing with pollen extract of the olive tree (prepared by Dr. Gutmann), which has approximately the same blossoming period, was negative.

SUMMARY

Four cases of Ailanthus glandulosa sensitivity are described. The pollen which is insect- and wind-borne is found in the air. More attention should be paid to this tree as a possible cause of hay fever.

REFERENCES

1. Blumstein, G. J.: Sensitivity to Ailanthus pollen. J. Allergy, 14:329-334, 1943.
2. Gutmann, M. J.: The first report on hay fever in Palestine. J. Allergy, 12: 182-187, 1941.
3. Gutmann, M. J.: Hay Fever in Palestine. Second report. Ann. Allergy, 8:345-349, 1950.
4. Urbach, E., and Gottlieb, P. M.: Allergy. p. 526. New York: Grune and Stratton, 1949.

SOUTHWEST ALLERGY FORUM

The seventeenth annual meeting of the Southwest Allergy Forum will be held at Hotel Beaumont, Beaumont, Texas, April 1-3, 1956. The first afternoon's program is in the form of a panel presentation on the changing picture of pollinosis in the Southwest. Monday's sessions will be devoted to a number of papers of general interest dealing with such subjects as corneal ulcers due to allergy, the basic problems of drug allergy, and gamma globulin and its therapeutic value in the asthmatic child. Dr. Jonathan Forman of Columbus, Ohio, will be the luncheon speaker and will address the meeting on "Working Classifications of Allergic Disorders." Panel discussions on "Infection in Respiratory Allergic Disease" and "Pediatric Allergy" occupy the program for Monday afternoon, the sessions being followed by a cocktail party and banquet. Histamine as an adjunct to allergic management, recurrent eczema of the hands of female patients, allergy management of dendritic ulcer, allergic dermatoses, insect allergy, and unusual allergies will be discussed on Tuesday. Such side activities as golf and fishing have been arranged, and there will be a special program for the ladies.

Preliminary Program

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY
April 15-17, 1956

and

TWELFTH ANNUAL CONGRESS
THE AMERICAN COLLEGE OF ALLERGISTS, INC.
April 18-20, 1956

Hotel New Yorker
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COMMITTEE AND BOARD MEETINGS

Saturday, April 14, 1956		
Board of Directors Meeting	8:00 a.m.	South Room
Board of Regents Meeting	10:00 a.m.	South Room
Tuesday, April 17		
Standardization (including subcommittees for Certification of Allergenic Extracts and Standardization of Aerosol Therapy)	9:00 a.m.	South Room
Pollen	9:00 a.m.	To be assigned
Bylaws	10:00 a.m.	To be assigned
Aerobiology	10:00 a.m.	To be assigned
Editorial Board	11:00 a.m.	Parlor B
New and Unused Therapeutics	2:00 p.m.	South Room
Public Education Committee	3:00 p.m.	Parlor B
Saturday, April 21		
New Board of Regents Meeting	9:00 a.m.	South Room

LAWRENCE J. HALPIN, M.D.
Cedar Rapids, Iowa
President, 1955-1956

Twelfth Annual Graduate Instructional Course in Allergy

(Preliminary Program—subject to minor changes)

SATURDAY, APRIL 14, 1956

Afternoon Registration

3:00—Registration—Mosaic Room

SUNDAY, APRIL 15, 1956

Morning Session—Mosaic Room

BASIC SCIENCES

Chairman: MORRIS A. KAPLAN, M.D., Chicago, Illinois

Co-Chairman: HOWARD G. RAPAPORT, M.D., New York, New York

8:00—Registration—Lower Lobby Foyer

8:55—Introduction and Announcements

9:00—History, Terminology, and Introduction to Allergy
M. MURRAY PESHKIN, M.D., Consulting Allergist, The Mount Sinai Hospital, New York, New York

9:30—Immunochemistry as Applied to Allergy
ELVIN A. KABAT, Ph.D.,* Department of Neurology and Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York

10:15—Physiology of Allergy; Theories of Mechanism, and Physiochemistry of Histamine Release
HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

10:55—Coffee Break, Auspices of the Women's Auxiliary

11:10—Pathology of Allergic and Collagen Diseases
MILTON G. BOHROD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

11:50—Stress Phenomena
WALTER S. ROOT, M.D.,* Professor of Physiology, College of Physicians and Surgeons, Columbia University, New York, New York

DEMONSTRATION

12:30-2:00 p.m.

Club Lounge

OFFICE AND LABORATORY PROCEDURES IN ALLERGY

STEPHEN D. LOCKEY, M.D., Chief, Department of Allergy, Lancaster General Hospital, Lancaster, Pennsylvania
SARAH R. LANDIS, Technologist

*By invitation

SUNDAY, APRIL 15, 1956

Afternoon Session—Mosaic Room

ALLERGIC RHINITIS

Chairman: HARRY L. ROGERS, M.D., Philadelphia, Pennsylvania

Co-Chairman: MARTYN A. VICKERS, M.D., Bangor, Maine

2:00—Botany

ROGER P. WODEHOUSE, Ph.D., Lederle Laboratories, American Cyanamid Company, Pearl River, New York

2:30—Environmental Allergens

CECIL M. KOHN, M.D., Chief of Allergy Department, Kansas City General Hospital, Kansas City, Missouri

3:00—Foods and Drugs as Allergens

NATHAN E. SILBERT, M.D., Lynn, Massachusetts. Chief of Allergy, Captain John Adams Hospitals, Lawrence Quigley Memorial Hospital and Soldiers' Home, Chelsea, Massachusetts

3:30—Treatment Conference Panel

Specific Immunization

Pollen

MERLE W. MOORE, M.D., Associate Clinical Professor of Medicine, Head of Division of Allergy, University of Oregon Medical School, Portland, Oregon

Inhalants

NATHAN SCHAFFER, M.D., Chief of Allergy, Orange Memorial Hospital, East Orange, New Jersey

Drugs

Steroids

EMANUEL SCHWARTZ, M.D., Division of Allergy, Department of Medicine, The Long Island College Hospital and the College of Medicine, State University of New York at New York.

Other Drugs

JACK A. RUDOLPH, M.D., Miami Beach, Florida

Rhinological

Symptomatic

KENNETH L. CRAFT, M.D., Department of Otolaryngology, Indiana University School of Medicine, Indianapolis, Indiana

Surgical

SAM H. SANDERS, M.D., Professor and Head of the Department of Otolaryngology, University of Tennessee College of Medicine, Memphis, Tennessee

Environmental Control

MILTON MILLMAN, M.D., San Diego, California

5:30—Discussion

PRELIMINARY PROGRAM

MONDAY, APRIL 16, 1956

Morning Session—Mosaic Room

BRONCHIAL ASTHMA

Chairman: HAL M. DAVISON, M.D., Atlanta, Georgia

Co-Chairman: MAYER A. GREEN, M.D., Pittsburgh, Pennsylvania

8:00—Registration—Lower Lobby Foyer

9:00—Physiology of Respiration

MORTIMER BADER, M.D.,* Director, Pulmonary Function Laboratory, The Mount Sinai Hospital, New York, New York

9:30—Classification, Causes, and Complications

LEON UNGER, M.D., Assistant Professor, Northwestern University School of Medicine; Attending Physician, Cook County Hospital, Chicago, Illinois

10:00—Differential Diagnosis

GILES A. KOELSCHE, M.D., Consultant, Division of Medicine, Mayo Clinic, Rochester, Minnesota

10:30—Coffee Break, Auspices of the Women's Auxiliary

10:45—Treatment Conference Panel

Specific Immunization (Dust, Molds, and Inhalants)

HOMER E. PRINCE, M.D., Professor of Medicine, Baylor University College of Medicine; Chief of Allergy, Hermann Hospital, Houston, Texas

Vaccine Therapy

MURRAY DWORETZKY, M.D., Department of Public Health and Preventive Medicine, New York, New York

Symptomatic Therapy (Potassium Iodide to Steroids)

PHILIP M. GOTTLIEB, M.D., Instructor in Medicine, University of Pennsylvania; Chief of Allergy, Kensington Hospital; Associate Allergist, Jewish Hospital; Allergist, Sidney Hillman Medical Center, Philadelphia, Pennsylvania

Mechanical and Physical Aids

ALVAN L. BARACH, M.D.,* Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York

Environmental and Climatologic

SOLOMON D. KLOTZ, M.D., Orlando, Florida; Consultant in Medicine, Patrick Air Force Hospital, Cocoa, Florida

12:00—Questions and Answers Panel

DEMONSTRATION

12:30-2:00 p.m.

Club Lounge

PATCH TESTS AND THEIR USE

MAX GROLNICK, M.D., Attendant in Charge, Allergy Division, Jewish Hospital; Associate Attending Physician, Chief of Allergy Department, Maimonides Hospital, Brooklyn, New York

*By invitation

PRELIMINARY PROGRAM

MONDAY, APRIL 16, 1956

Afternoon Session—Mosaic Room

ECZEMA AND ALLERGIC SKIN DISORDERS

Chairman: SAMUEL M. PECK, M.D., New York, New York

Co-Chairman: SUSAN DEES, M.D., Durham, North Carolina

2:00—Pathology of Allergic Skin Disorders

SAMUEL M. PECK, M.D., Director, Department of Dermatology, The Mount Sinai Hospital; Associate Clinical Professor of Dermatology, Columbia University College of Physicians and Surgeons, New York, New York

2:30—Classification and Causes of Eczema in Infants

JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-chief, Genesee Hospital, Rochester, New York

2:45—Classification and Causes of Eczema in Adults

RUDOLF L. BAER, M.D., Associate Professor, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, New York, New York

3:00—Diagnosis and Tests in Contact Dermatitis

GEORGE L. WALDBOTT, M.D., Instructor, Wayne University College of Medicine, Detroit, Michigan

3:15—Diagnosis and Tests in Non-Contact Dermatitis

MAURICE C. BARNES, M.D., Lecturer in Dermatology and Allergy, Providence Hospital School of Nursing; Consultant in Dermatology, Waco Veterans Hospital and James Connally Air Force Base; Attendant in Dermatology, Hillcrest, Providence, and City Hospitals, Waco, Texas

3:30—Conference Treatment Panel

Topical Applications

MORRIS LEIDER, M.D., Associate Professor, Department of Dermatology and Syphilology, New York Post-Graduate Medical School, New York University-Bellevue Medical Center, New York, New York

Environmental Contactants

GEORGE L. WALDBOTT, M.D., Instructor, Wayne University College of Medicine, Detroit, Michigan

Steroid Therapy

RUDOLF L. BAER, M.D., Associate Professor, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, New York, New York

Dietary Management in Children

LLOYD S. NELSON, M.D., Assistant to Chief of Pediatric Allergy Clinic, University of Minnesota; Chief of Pediatric Section, St. Barnabas Hospital, Minneapolis, Minnesota

5:30—Questions and Answers Panel

7:00—Informal Buffet Supper—Mosaic Room

Small discussion groups with individual instructors

PRELIMINARY PROGRAM

TUESDAY, APRIL 17, 1956

Morning Session—Mosaic Room

SPECIAL PROBLEMS IN ALLERGY

Chairman: ETHAN ALLAN BROWN, M.R.C.S. (England) and L.R.C.P. (London), Boston, Massachusetts

Co-Chairman: JAMES MANSMANN, M.D., Pittsburgh, Pennsylvania

8:00—Registration—Lower Lobby Foyer

9:00—Importance of the Initial Interview

JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

9:25—Office Management of the Allergic Patient

JOHN D. GILLASPIE, M.D., Director, Boulder Clinic, Boulder, Colorado

9:50—Occupational and Industrial Allergy

STEPHEN D. LOCKEY, M.D., Allergist, Lancaster General Hospital, Lancaster, Pennsylvania

10:15—Psychosomatic and Psychological Aspects of Allergy

HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

10:40—Coffee Break, Auspices of the Women's Auxiliary

10:55—Local and Constitutional Reactions

MORRIS A. KAPLAN, M.D., Assistant Professor of Medicine, Chicago Medical School, Director of Allergy Research Unit, Chicago Medical School and Mount Sinai Medical Research Foundation, Chicago, Illinois

11:15—Bacterial Allergy

HERMANN BLATT, M.D., Cincinnati, Ohio

11:40—Endocrine Aspects of Allergy

S. H. JAROS, M.D., Harlingen, Texas

12:05—Prophylaxis in Childhood Allergy

HOWARD G. RAPAPORT, M.D., Pediatrician in Charge, Pediatric Allergy Clinic, The Mount Sinai Hospital, New York, New York

DEMONSTRATION

12:30-2:00 p.m.

Club Lounge

METHODS OF TESTING

(Scratch, Intradermal, Insufflation, Ophthalmic)

STEPHEN D. LOCKEY, M.D., Chief, Department of Allergy, Lancaster General Hospital, Lancaster, Pennsylvania
SARAH R. LANDIS, Technologist

PRELIMINARY PROGRAM

TUESDAY, APRIL 17, 1956

Afternoon Session—Mosaic Room

MISCELLANEOUS ALLERGY

Chairman: J. Warrick Thomas, M.D., Richmond, Virginia

Co-Chairman: James E. Stroh, M.D., Seattle, Washington

2:00—Hematologic Aspects of Allergy

Frank Bassen, M.D.,* Attending Physician, The Mount Sinai Hospital, Director, Hematology Laboratory, and Assistant Hematologist in Charge of Clinic, Beekman-Downtown Hospital, New York, New York

2:30—Evaluation of Headache in Allergy

Henry D. Ogden, M.D., Assistant Professor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

3:00—Ocular Allergy

Frederick H. Theodore, M.D.,* Instructor in Ophthalmology, Columbia University College of Physicians and Surgeons and New York University; Adjunct Ophthalmologic Surgeon, The Mount Sinai Hospital, New York, New York

3:30—Gastrointestinal and Food Allergy

Albert H. Rowe, M.D., Allergist, Samuel Merritt Hospital, Oakland Naval Hospital, Oakland; Allergist, Cowell Hospital, Berkeley; Lecturer in Medicine, University of California Medical School, San Francisco, California

4:00—Urticaria, Angioedema, and Serum Sickness

Orval R. Withers, M.D., Kansas City, Missouri; Head of Allergy Clinic, Associate Clinical Professor of Medicine, University of Kansas School of Medicine, Kansas City, Kansas

4:30—Drug Allergy

J. Warrick Thomas, M.D., Assistant Professor, Clinical Medicine, Medical College of Virginia, Richmond, Virginia

4:50—Insect Allergy

Richard L. Etter, M.D., Instructor in Clinical Medicine, Baylor University College of Medicine; Associate in Allergy, Hermann Hospital, Houston, Texas

5:10—Physical Allergy

R. Dale Dickson, M.D., Topeka, Kansas

6:00—Cocktail Party, Courtesy of the New York Allergy Society
Boston-Washington Rooms

STEREO PICTURE PRESENTATION—Mosaic Room
7:00-9:00 p.m.

COMMON HAY FEVER WEEDS AND CHARTS SHOWING DISTRIBUTION OF EACH PLANT

Mr. Hugh Graham and Associates

Graham Laboratories, Dallas, Texas

*By invitation

SUNDAY THROUGH THURSDAY, APRIL 15-19, 1956

Club Lounge—(Except Tuesday evening)

OFFICE AND LABORATORY PROCEDURES

Sunday, April 15 **12:30–2:00 p.m.**	**Office and Laboratory Procedures in Allergy. Practical Demonstrations** STEPHEN D. LOCKEY, M.D., and SARAH R. LANDIS, Technologist
Monday, April 16 **12:30–2:00 p.m.**	**Patch Tests and Their Use. A Demonstration** MAX GROLNICK, M.D.
Tuesday, April 17 **12:30–2:00 p.m.**	**Methods of Testing (Scratch, Intradermal, Insufflation, Ophthalmic). A Demonstration** STEPHEN D. LOCKEY, M.D., and SARAH R. LANDIS, Technologist

Mosaic Room

Tuesday, April 17 **7:00–9:00 p.m.**	**Stereo Pictures of the Common Hay Fever Weeds and Charts Showing Distribution of Each Plant** HUGH GRAHAM and Associates

Club Lounge

Wednesday, April 18 **12:30–2:00 p.m.**	**Nebulizers and Their Use. A Demonstration** HAROLD A. ABRAMSON, M.D.
Thursday, April 19 **12:30–2:00 p.m.**	**Miscellaneous Office Procedures. Practical Demonstrations** STEPHEN D. LOCKEY, M.D., and SARAH R. LANDIS, Technologist

The fee for the Instructional Course is $45 for three days, $30 for two days, and $15 for one day. All College members in good standing may take the entire course for $25. These fees do not include the price of the buffet supper on Monday evening.

The Instructional Course program meets the American Academy of General Practice standards of postgraduate study for Category 2 credit for its members.

TECHNICAL EXHIBITS

During the midmorning and midafternoon of each of the three days of the scientific program, time has been allotted for visiting the exhibits. The chairmen presiding at the morning and afternoon sessions are instructed to call a recess at the times indicated on the program. In addition, at the close of each day's session, chairmen will again invite registrants to visit the booths of our exhibitors. This is a courtesy we must extend, for without the exhibitors it would be impossible to finance such a meeting as ours.

You will find these technical exhibits worthy of your time and interest. The representatives in charge of the individual exhibits will be pleased to receive any suggestions or comments you choose to make. Many of these exhibitors are advertisers in the ANNALS OF ALLERGY and/or Sustaining Members of The American College of Allergists.

Your cooperation in showing our appreciation to the technical exhibitors is most earnestly requested.

Twelfth Annual Congress

(Preliminary Program—subject to minor changes)

TUESDAY, APRIL 17, 1956

2:00—Registration—Lower Lobby Foyer

6:00—Cocktail Party—Courtesy, New York Allergy Society
Boston-Washington Rooms

WEDNESDAY, APRIL 18, 1956

Morning Session—Grand Ballroom

GENERAL SESSION

Chairman: L. O. Dutton, M.D., El Paso, Texas
Co-Chairman: David Thomas, M.D., Augusta, Georgia

9:00—Address of Welcome
Murray M. Albert, M.D., Brooklyn, New York. President, New York Allergy Society

9:05—Response
Lawrence J. Halpin, M.D., Cedar Rapids, Iowa. President, The American College of Allergists

9:10—Pollen Allergy as a Cause of Gastrointestinal Symptoms
Albert H. Rowe., and Albert Rowe, Jr., Oakland, California
Open Discussion

9:30—Controlled Studies of Topical Medications in Nasal Allergy
Henry D. Ogden, M.D., and Jack Anderson, M.D., New Orleans, Louisiana
Open Discussion

9:50—Three Dimensional Projection Stereo-Kodachrome Pictures and Distribution Maps of Common Plant Allergens
Hugh Graham,* Dallas, Texas, and Tom Stemen, Oklahoma City, Oklahoma

10:20—RECESS TO VISIT EXHIBITS
Chairman: Cecil M. Kohn, M.D., Kansas City, Missouri
Co-Chairman: Mason I. Lowance, M.D., Atlanta, Georgia

10:40—Content Analysis of Somatic Symptoms in 327 Verbatim Psychotherapeutic Interviews in an Allergic Patient
H. A. Abramson, M.D., H. H. Gettner, M.A., and B. Sklarofsky, B.A., New York, New York
Open Discussion

11:20—Anaphylactic Reactions to Penicillin
G. A. Peters, M.D., Lowell L. Henderson, M.D., and Louis E. Prickman, M.D., Rochester, Minnesota
Open Discussion

11:40—Observations on Potassium Iodide Sensitivity
Lamar B. Peacock, M.D., and Hal M. Davison, M.D., Atlanta, Georgia
Open Discussion

12:00—Anaphylactic Shock Due to the Use of Cosmetics
George R. Laub, M.D., Columbia, South Carolina
Open Discussion

DEMONSTRATION

12:30-2:00 p.m.

Club Lounge

NEBULIZERS AND THEIR USE

Harold A. Abramson, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

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*By invitation

PRELIMINARY PROGRAM

WEDNESDAY, APRIL 18, 1956

Afternoon Session—Grand Ballroom

Chairman: WILLIAM BROWNING, M.D., Shreveport, Louisiana

Co-Chairman: JOHN D. GILLASPIE, M.D., Boulder, Colorado

2:00—Nasal Reactions to Pollen and Odor of Roses
MILTON M. HARTMAN, M.D., San Francisco, California
Open Discussion

2:20—The Use of a New Respiratory Index for the Evaluation of Xanthine Drugs in Chronic Pulmonary Disease
S. WILLIAM SIMON, M.D., Dayton, Ohio
Open Discussion

2:40—The Nature of Antibody Cross Reactions as Disclosed by Studies on Blood Group Antibodies, and Their Significance in Allergy
ALEXANDER S. WIENER, M.D.,* and IRVING B. WEXLER, M.D.,* Brooklyn, New York
Open Discussion

3:10—RECESS TO VISIT EXHIBITS
Chairman: M. MURRAY PESHKIN, M.D., New York, New York
Co-Chairman: HOWARD G. RAPAPORT, M.D., New York, New York

3:30—New Bronchoscopic Studies in Experimental and Clinical Asthma. A motion picture in color
Prepared by B. N. HALPERN, M.D., and J. M. DUBOIS DE MONTREYNAUD, M.D., Hospital Broussais, Paris, France
(This presentation demonstrates the use of a newly invented self-illuminated bronchoscope, and shows the actual effects of sympathetic and parasympathetic stimulation on the bronchi, as well as the effects of medication.)
Comments: ETHAN ALLAN BROWN, M.R.C.S. (England) and L.R.C.P. (London), Boston, Massachusetts
Open Discussion

4:00—Allergy in Ophthalmology
HOWARD C. LEOPOLD, M.D., and IRVING H. LEOPOLD, M.D., Philadelphia, Pennsylvania
Open Discussion

4:20—Eczema of the Eyelids (Kodachromes)
FREDERICK H. THEODORE, M.D.,* New York, New York
Open Discussion

4:45—ACTH: Its Use by the Slow Intravenous Infusion Method for the Relief of Intractable Bronchial Asthma
STEPHEN D. LOCKEY, M.D., Lancaster, Pennsylvania
Open Discussion

5:00—A Method of Reducing Reactions in Intravenous Pyelography with an Antihistaminic Agent
MAURY D. SANGER, M.D., and DAVID E. EHRLICH, M.D., New York, New York
Open Discussion

*By invitation

WEDNESDAY, APRIL 18, 1956

Evening Session—Grand Ballroom—8:00-10:00 p.m.

THE ASSOCIATION OF ALLERGISTS FOR MYCOLOGICAL INVESTIGATIONS, INC.

President: HOMER E. PRINCE, M.D., Houston, Texas

Secretary-Treasurer: SIM HULSEY, M.D., Fort Worth, Texas

The scientific meeting of The Association of Allergists for Mycological Investigations, Inc., will consist essentially of an informal question and answer period. Questions relating to mold allergy may be presented from the floor or may be mailed to one of the above officers in advance of the meeting. The questions will be assigned to members of a question and answer panel for opening the discussions. All physicians interested in mold allergy are invited to attend and take part in the discussions.

OR

WEDNESDAY, APRIL 18, 1956

Evening Session—South Room—8:00-10:00 p.m.

MEDICAL WRITERS' WORKSHOP

Chairman: JONATHAN FORMAN, M.D., Worthington, Ohio

How Not To Write Medical Papers

ETHAN ALLAN BROWN, M.R.C.S. (England), and L.R.C.P. (London)
Boston, Massachusetts

PRELIMINARY PROGRAM

THURSDAY, APRIL 19, 1956

Morning Session—Grand Ballroom

Chairman: HARRY L. ROGERS, M.D., Philadelphia, Pennsylvania

Co-Chairman: ORVAL R. WITHERS, M.D., Kansas City, Missouri

9:00—Rehabilitation of Intractable Asthma of Childhood
M. MURRAY PESHKIN, M.D., New York, New York
Open Discussion

9:30—Considerations of Special Interest to the Allergist on the Composition and Production of Poliomyelitis Vaccine
M. Z. BIERLY, JR., M.D.,* Philadelphia, Pennsylvania
Open Discussion

10:00—RECESS TO VISIT EXHIBITS
Chairman: JOHN H. MITCHELL, M.D., Columbus, Ohio
Co-Chairman: BOEN SWINNY, M.D., San Antonio, Texas

10:20—The Allergy of Infection. Theory and Implications
MORRIS LEIDER, M.D., New York, New York
Open Discussion

10:40—Auto-erythrocyte Sensitization: A Case Report
PHILIP M. GOTTLIEB, M.D., SONIA STUPNIKER, M.D., and IRVING WOLDOW, M.D., Philadelphia, Pennsylvania

11:00—Sensitivity of Human Leukocytes to Microorganisms and Their Products I. The Blatt, Nantz, and Rehm Techniques
MORRIS SCHERAGO, B.S., Lexington, Kentucky
Open Discussion

11:20—Studies on Antibody Response to Yeast in Patients with Bronchial Asthma
MILTON GOLDIN, M.S., ARNALDO LIBRETTI, M.D., and MORRIS A. KAPLAN, M.D., Chicago, Illinois
Open Discussion

11:35—Avenues of Research in Allergy
STANLEY F. HAMPTON, M.D.,* President, American Academy of Allergy, St. Louis, Missouri

DEMONSTRATION

12:30-2:00 p.m.

Club Lounge

MISCELLANEOUS OFFICE PROCEDURES

STEPHEN D. LOCKEY, M.D., Chief, Allergy Department, Lancaster General Hospital, Lancaster, Pennsylvania

SARAH R. LANDIS, Technologist

*By invitation

PRELIMINARY PROGRAM

THURSDAY, APRIL 19, 1956

Afternoon Session—Grand Ballroom

Chairman: J. Warrick Thomas, M.D., Richmond, Virginia

Co-Chairman: Giles A. Koelsche, M.D., Rochester, Minnesota

2:00—Presidential Address
Lawrence J. Halpin, M.D., Cedar Rapids, Iowa

2:20—Introduction of ETHAN ALLAN BROWN, M.R.C.S. (England) and L.R.C.P. (London), President-Elect, Boston, Massachusetts

2:30—A New Theory of the Allergic Phenomena

Guest Speaker

Prof. M. G. Sevag, B.A., Ph.D.,* Department of Microbiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

3:30—RECESS TO VISIT EXHIBITS

4:00—Business Meeting—Grand Ballroom

6:30—Cocktail Party. Courtesy, The Schering Corporation
Terrace Room

FRIDAY, APRIL 20, 1956

Morning Session—Grand Ballroom

DERMATOLOGY SESSION

Chairman: Norman B. Kanof, M.D.,* New York Post-Graduate Medical School, New York University-Bellevue Medical Center, New York, New York

9:00—Allergic Contact Stomatitis and Cheilitis
Alexander A. Fisher, M.D., New York Post-Graduate Medical School, New York University-Bellevue Medical Center, New York, New York

9:30—Observations Concerning the Nature of Itching
Walter B. Shelley, M.D.,* University of Pennsylvania Medical School, Philadelphia, Pennsylvania

10:00—RECESS TO VISIT EXHIBITS

10:30—Pathogenic and Saphrophytic Fungi in the Production of Allergic Dermatitis
Otis F. Jillson, M.D.,* The Hitchcock Clinic, Hanover, New Hampshire

11:00—Hyposensitization Against Rhus Dermatitis
Albert M. Kligman, M.D.,* University of Pennsylvania Medical School, Philadelphia, Pennsylvania

*By invitation

PRELIMINARY PROGRAM

FRIDAY, APRIL 20, 1956

Morning Session—Empire Room

OPHTHO-OTOLARYNGOLOGIC SESSION

Chairman: SAM H. SANDERS, M.D., Memphis, Tennessee

9:00—The Importance of Nutrition in Infection and Allergy
GRANVILLE F. KNIGHT, M.D., President, American Academy of Nutrition, Santa Barbara, California

9:30—Histopathology of Nasal Allergy
RAYMOND S. ROSEDALE, M.D.,* Consultant, Pomerene Hospital, Millersburg; Memorial Hospital, Dover; and Twin City Hospital, Dennison; Court Staff in Otolaryngology and Plastic Surgery, Aultman Hospital; Resident in Otolaryngology, Barnes, McMillan, St. Luke's, and Children's Hospitals, Canton, Ohio

10:00—Question and Answer Period. Discussion from the floor is encouraged.

10:45—Panel: The Importance of Infection in Otolaryngologic Allergy
JOSEPH GOLDMAN, M.D.,* Head of Department of Otolaryngology, The Mount Sinai Hospital, New York, New York
SHEPPARD SIEGAL, M.D.,* The Mount Sinai Hospital, New York, New York
HUGH A. KUHN, M.D., Memorial, St. Margaret's, St. Catherine's, Ingalls, Memorial, and Our Lady of Mercy Hospitals, Hammond, Indiana
KENNETH L. CRAFT, M.D., Department of Otolaryngology, Indiana University School of Medicine, Indianapolis, Indiana
LOUIS SILCOX, M.D.,* Dean of Otolaryngology, University of Pennsylvania School of Medicine; Chief, Ear, Nose and Throat Service, Lankenau Hospital, Philadelphia, Pennsylvania

12:30—Luncheon, Business Session, and Election of Officers—Panel Room

FRIDAY, APRIL 20, 1956

Afternoon Session—Grand Ballroom

PEDIATRIC ALLERGY SESSION

Chairman: HOWARD G. RAPAPORT, M.D., New York, New York

8:00—Breakfast—Mosaic Room—Courtesy, Prescription Products Division, The Borden Company.

9:00—A Practical Plan for the Management of Eczema in Infants and Children
WILLIAM MESSER, M.D., The Mount Sinai Hospital, New York, New York

9:20—A Plea for More Cooperation Between the Internist, the Gastroenterologist, and the Allergist in the Management of Chronic Colitis.
EDWARD SCOTT O'KEEFE, M.D., Member of the Board of Consultation of the Massachusetts General Hospital, Boston; Consultant in Allergy, Lynn Hospital, Lynn, Massachusetts

9:40—A Study on the Allergic Syndrome in Children with Celiac Disease
DOUGLAS E. JOHNSTONE, M.D., Assistant Pediatrician, Strong Memorial and Genesee Hospitals; Attending Pediatrician, Pediatric Allergy Clinic, Strong Memorial Hospital; Instructor in Pediatrics, University of Rochester School of Medicine, Rochester, New York

10:00—Chest Film and the Asthmatic Child
HAROLD I. LECKS, Children's Hospital, Philadelphia, Pennsylvania.

10:20—RECESS TO VISIT EXHIBITS. Coffee, Courtesy of The Borden Company

*By invitation

10:40—Cellular Aspects of Antibody Production

ALBERT H. COONS, M.D.,* Visiting Professor of Bacteriology and Immunology, Harvard Medical School, Boston, Massachusetts

11:20—The Clinical Importance of Food Dislikes in Allergic Children

MARY S. BOYDEN, M.D.,* Fellow in Pediatric Allergy, and JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York (Paper to be presented by Dr. Boyden)

11:40—The Effect of Prolonged Cortisone Therapy on Growth and Skeletal Maturation in Allergic Children

F. M. BLODGETT, M.D.*; M. IEZORRI, M.D.*; D. GRIBITZ, M.D.*; L. B. BURGIN, M.D.*; and N. B. TALBOTT, M.D.,* The Children's Medical Service, Massachusetts General Hospital, Boston, Massachusetts; and the Department of Pediatrics, The Mount Sinai Hospital, New York, New York. (Dr. Gribitz will present the paper)

12:30—Luncheon—Mosaic Room. Open to all members and guests

Guest Speaker: BELA SCHICK, M.D.,* Professor of Pediatrics, Albert Einstein Medical School; Director of Pediatrics, Beth-El Hospital; and Consultant in Pediatrics at The Mount Sinai, Seaview, and Beth-David Hospitals and New York Infirmary, New York, New York

"Physiological and Pathological Allergy"

FRIDAY, APRIL 20, 1956

Afternoon Session—Grand Ballroom

PSYCHOSOMATIC SESSION

Chairman: HYMAN MILLER, M.D., Beverly Hills, California

2:00—Brief Psychotherapy in an Allergy Clinic

HYMAN ASHMAN, M.D.,* Brooklyn, New York

2:20—Is Chronic Urticaria an Allergic Disorder?

JOHN H. MITCHELL, M.D., and DOUGLAS L. SMITH, M.D., Columbus, Ohio

2:40—A Psychotherapist's Integration into an Allergy Practice

BENNETT KRAFT, M.D., Indianapolis, Indiana

3:00—RECESS TO VISIT EXHIBITS

3:10—Management of Emotional Problems in the Allergist's Office

HYMAN MILLER, M.D., Beverly Hills, California

3:30—Management of the Parent Relationship to the Allergic Child

DOROTHY W. BARUCH, Ph.D.,* Beverly Hills, California

3:50—Research on Maternal Attitudes, Prepartum and Postpartum

MARGARET E. FRIES, M.D.,* Practicing Psychoanalyst for Adults and Adolescents; Attending Psychiatrist, Hillcrest Hospital; Director of Research Project on Integrated Development, New York Infirmary, and Producer of Films on Integrated Development, New York University Film Library, New York, New York.

(A five-minute discussion period will follow each paper.)

*By invitation

Women's Auxiliary

SUNDAY, APRIL 15

Visits to Frick Museum of Art (Standing Collections) 1:00-5:00 p.m.; Metropolitan Museum of Art (Luncheon 1:00-3:00 p.m., Lecture 3:00 p.m.); The Cloisters, Uptown Branch of Metropolitan (Medieval Art).

MONDAY, APRIL 16

Entertainment available: TV Tickets; Hayden Planetarium; Radio City NBC Studio Television Tour; Rockefeller Center Guided Tour; Empire State Building Observation; Guided Tour of United Nations Headquarters; Cruise around Manhattan Island (Box Lunch); and Good Housekeeping Tour.

TUESDAY, APRIL 17

Visits to: Museum of Modern Art, 12:00 noon (Permanent exhibition, sculpture, poster show, movies, tea), and to Whitney Museum. 6:00 p.m., Cocktail Party, Courtesy of New York Allergy Society, Boston-Washington Rooms, Hotel New Yorker.

WEDNESDAY, APRIL 18

9:00—Registration and payment of dues. 10:00—Second Annual Business Meeting of the Women's Auxiliary of The American College of Allergists. 12:00—Luncheon at Hotel Plaza, White and Gold Room. Speaker: Dr. Horace S. Baldwin, President American Foundation for Allergic Diseases. Entertainment and musical presentation of "Damn Yankees."

THURSDAY, APRIL 19

10:30 a.m.—Visit to United Nations Session, with luncheon in the Delegates' Dining Room at 11:45, guided tour at 1:00, and lecture at 2:00 p.m. 3:00-5:00—Tea for husbands and wives, Hospitality Room. 6:30 p.m.—Cocktail Party. Courtesy The Schering Corporation, Terrace Room, Hotel New Yorker.

FRIDAY, APRIL 20

Breakfast at B. Altman & Co. (Charleston Garden), prizes, and fashion show.

3:00-5:00—Teas for husbands and wives, Hospitality Room.

NOTE: Reservations for the Hotel Plaza luncheon, the United Nations Session, and the breakfast should be made in advance.

Orders for theater tickets will be taken on registration day or may be made in advance by mail to Theater Party Enterprises, Att'n T. K. Ellis, 1564 Broadway, New York 36, New York. A $5.00 deposit must accompany a request for tickets, and Theater Party Enterprises makes a service charge of $1.00 plus 10c tax. Tickets will be mailed to the member or left at the box office.

The ladies of the Auxiliary will serve and assist at the Coffee Breaks to be held for the physicians attending the Instructional Course on Sunday, Monday, and Tuesday. Volunteers who wish to offer their services may register at the Hospitality Room at the Hotel New Yorker. This room will be maintained by the Hostess Committee during the meeting; refreshments will be served, messages may be left, and registration and payment of dues may also be made.

It is the aim of the Hostess Committee to be completely at the service of the members of the Women's Auxiliary and their guests.

Technical Exhibits

Almay Beauty Preparations, Division of Schieffelin & Co.	New York, New York
Aveeno Corporation	New York, New York
Beech-Nut Packing Company	New York, New York
Bilhuber-Knoll Corporation	Orange, New Jersey
The Borden Company	New York, New York
Brewer & Company	Worcester, Massachusetts
C. A. Brinkman & Company	Great Neck, New York
Bruce Publishing Company	St. Paul, Minnesota
Burroughs Wellcome & Co. (U.S.A.), Inc.	Tuckahoe, New York
Center Laboratories, Inc.	Port Washington, New York
Ciba Pharmaceutical Products, Inc.	Summit, New Jersey
The Coca-Cola Company	Atlanta, Georgia
Joseph K. Dennis Co.	Chicago, Illinois
Desitin Chemical Company	Providence, Rhode Island
The DeVilbiss Company	Somerset, Pennsylvania
Doho Chemical Corporation	New York, New York
Dome Chemicals, Inc.	New York, New York
Duke Laboratories, Inc.	Stamford, Connecticut
Eisele & Company	Nashville, Tennessee
J. H. Emerson Company	Cambridge, Massachusetts
Endo Products, Inc.	Richmond Hill, New York
Gerber Products Company	Fremont, Michigan
Graham Laboratories	Dallas, Texas
Grune & Stratton, Inc.	New York, New York
Hollister-Stier Laboratories	Philadelphia, Pennsylvania
Jackson-Mitchell Pharmaceuticals, Inc.	Culver City, California
Luzier's, Inc.	Kansas City, Missouri
Marcelle Cosmetics, Inc.	Chicago, Illinois
McNeil Laboratories, Inc.	Philadelphia, Pennsylvania
Nepera Chemical Co., Inc.	Yonkers, New York
Pfizer Laboratories	Brooklyn, New York
Ralston Purina Company	St. Louis, Missouri
Raytheon Manufacturing Company	Waltham, Massachusetts
Rexair Division, Martin-Parry Corp.	Toledo, Ohio
Sandoz Pharmaceuticals	New York, New York
Schering Corporation	Bloomfield, New Jersey
G. D. Searle & Co.	Chicago, Illinois
Sharp & Dohme	Philadelphia, Pennsylvania
Stiefel Medicinal Soap Company, Inc.	Oak Hill, New York
Travenol Laboratories, Inc. (Subsidiary of Baxter Laboratories, Inc.)	Morton Grove, Illinois
Union Pharmaceutical Co. (Subsidiary of The Schering Corpn.)	Bloomfield, New Jersey
United States Tobacco Company	New York, New York
Vaponefrin Company	Upper Darby, Pennsylvania
Walton Laboratories, Inc.	Irvington, New Jersey
Alan Wende Company, Incorporated	Mineola, New York
Westwood Pharmaceuticals	Buffalo, New York
Winthrop Laboratories, Inc.	New York, New York
Wyeth Laboratories	Philadelphia, Pennsylvania

DIPHEMANIL METHYLSULFATE CREAM PLAIN AND WITH HYDROCORTISONE IN THE TREATMENT OF VARIOUS SKIN DISEASES

F. W. WITTICH, M.D., F.A.C.A.
Minneapolis, Minnesota

FOLLOWING the discovery of epinephrine (Abel, 1900) and its variants, with their beneficial effects in the relief of distressing allergies, reports by Dale[1] and Loewi[2] appeared on another agent affecting the autonomic nervous system, acetylcholine. Acetylcholine serves as a chemical mediator of terminal parasympathetic nerve impulses. Anticholinergic drugs were developed to block the action of acetylcholine with its peripheral dilator action on certain blood vessels, its effect on parasympathetically innervated structures through a peripheral action, and its stimulating effect on autonomic ganglia.

The action of acetylcholine in the body is controlled by cholinesterase. When the acetylcholine-cholinesterase balance is disturbed, as by a severe antigen-antibody reaction, and the enzyme is deficient, it is logical for certain anticholinergic agents to prove beneficial as adjuncts in the treatment of the allergic manifestations.

Diphemanil methylsulfate, reported by Margolin et al,[3] primarily blocks the action of acetylcholine. Numerous reports[4-12] have showed its favorable action when given orally, parenterally, and topically in hyperhidrosis[6,11] and in itching skin conditions such as the various types of contact dermatitis[4,5,7-10] and eczema, and particularly in cases where the skin was moist.

This report deals entirely with personal observations on the topical use of diphemanil (Prantal®) methylsulfate cream*, containing 2 per cent of the agent, and Prantal with Cortifan® cream*, containing 2 per cent diphemanil methylsulfate with 1 per cent hydrocortisone.

Since the immediate needs of the patient were the primary consideration, the two anticholinergic creams were used topically in a variety of skin conditions without prior consideration as to whether or not allergy was an etiologic factor. The results were encouraging enough to warrant their trial in other irritating skin lesions. Remembering that "All is not allergy that itches" was helpful in experimenting with nonallergic or borderline allergic conditions. Sometimes when standard therapy was unsatisfactory or failed in a particular patient, one of the creams was used.

Great relief was obtained in numerous dermatologic conditions seen in a varied practice with the plain diphemanil methylsulfate cream. The beneficial results coincided with those of previous reports on such conditions

*Supplied by George Babcock, Jr., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

as the contact dermatitides, eczema, exudative neurodermatitis, hyperhidrosis, and pruritic syndromes so treated. The effects were determined of this therapy on skin conditions such as hives, the dry skin of old age, sunburn, abrasions, chafing, scalds, diaper rash, athlete's foot, dermatitis medicamentosa, dermatitis due to irradiation, pruritus hiemalis, seborrhea of the acute intertriginous type (including that of the groin, the gluteal cleft, retroauricular areas, and the external auditory canals), stasis eczema, various forms of erythema, lichen planus, erythema multiforme, and chicken pox.

Judgment had to be exercised in applying other therapeutic measures concomitantly. For example, whenever possible the use of antibiotics was avoided. This report deals with some skin conditions on which there has heretofore been little emphasis, and with the application of these two creams containing an anticholinergic agent to a variety of skin lesions.

The following are typical case reports.

RECURRENT HIVES

Case 1.—A six-year-old boy with hyperplastic sinusitis was found to be sensitive to certain foods, especially chocolate and eggs, and to barbiturates as well. When the sinusitis was active, the food sensitivity became more marked, and giant hives with intense itching appeared. Numerous antihistamines, tried along with avoidance measures, delayed the reaction but did not give the immediate relief for which a suffering child is always impatient. Since treatment with a lotion containing a potentially sensitizing antipruritic such as phenol or benzocaine seemed inadvisable, diphemanil methylsulfate cream was applied. Relief was afforded almost immediately and lasted for three to four hours. The intolerable itching and its aggravation by scratching were eliminated, and the hives subsided earlier than in former attacks. The prompt relief reduced the fear of possible recurrences, which undoubtedly had a beneficial psychotherapeutic effect upon the patient.

Eighteen other patients of various ages with urticaria obtained relief rapidly with this cream. Two patients with severe angioedema, which in one resulted from the ingestion of certain foods and from the inhalation of gymnasium dust, and in the other from foods alone, obtained satisfactory relief with the cream applied every four hours. In a few patients, the combination with hydrocortisone gave better results. The causes of the urticarial response of the patients included plant contact (nettle rash), insect bites, a jellyfish sting, drugs and sera, foods, sudden thermal changes, and emotional factors.

DRY SKIN

The ichthyotic or dry skin of old age, eczema, winter itch (pruritus hiemalis), and sunburn (solar dermatitis) were also treated with diphemanil methylsulfate cream. Dry skin usually itches only during cold weather. During the winter months in the northern United States and in Canada, dry skin accompanied by intolerable itching is encountered fre-

quently. Secondary infections from excoriations occur repeatedly, and, in the older age group, loss of sleep because of them may impair the general health.

The anhidrotic effect of diphemanil methylsulfate on dry skin is easily overcome by a light application of Aquaphor in a 1 per cent water-in-oil base, Nivea, or Eucerine (Duke), to the affected areas. Such a water-in-oil base also increases the penetration of the cream and serves as a cleansing agent, replacing soap or detergents that may aggravate the dryness. The prior application of one of these preparations has been advantageous when diphemanil methylsulfate cream has been used to overcome the pruritus or dermatitis accompanying a dry skin.

The use of protective suntan lotions or creams is advisable in patients sensitive to sunlight, but many light-sensitive individuals either neglect protective measures or overexpose their bodies to actinic rays. The resulting blistering or deep sunburn causes extreme discomfort. Diphemanil methylsulfate cream affords quick relief in sunburn. At the desquamating stage, it is preceded by an application of Aquaphor in a water-in-oil emulsion or Eucerine.

Case 2.—A fifty-nine-year-old iron mine worker in northern Minnesota had always had some dryness of the skin, but in recent years the dryness had increased. During the winter months, although the patient was suitably clothed, an intolerable itching developed on his legs, primarily over the calves and buttocks, his hands, and the backs of his shoulders. Numerous antipruritic lotions and ointments were tried, and one containing 3 per cent benzocaine intensified the itching. The use of soaps was discontinued. Before exposure to cold and at any time when itching was noticed, a thin layer of Eucerine was applied and followed by the application of diphemanil methylsulfate cream. Complete relief resulted from this regimen.

The pruritus of dry skin eczemas was treated similarly along with routine measures. In these cases, however, diphemanil methylsulfate with hydrocortisone cream gave results superior to those obtained with the plain cream.

ABRASIONS

The frequent falls of children sometimes result in fairly extensive superficial skin abrasions that become extremely painful as the thin layer of deep skin oozes and burns.

Case 3.—An eight-year-old boy suffered extensive abrasions of both forearms and of the extensor surfaces of the knees and shins as the result of landing on the ground rubble at the end of a playground slide. All of the available remedies applied as first aid would have aggravated the condition. Diphemanil methylsulfate with hydrocortisone cream was tried with dramatic relief. No infection developed and application of the cream was continued until dressings were no longer necessary. This cream has also proved highly beneficial in the treatment of abrasions in many other young children.

INTERTRIGO AND DIAPER RASH

Intertrigo, commonly known as chafing, is prevalent in children and occurs where two moist surfaces rub together, as in the groin between the inner thighs, and on other flexural surfaces of infants. Soiled diapers remaining on an infant are a common cause of this condition and of diaper rash. If intertrigo or diaper rash is neglected, moist eczema may develop. Nothing seems to give more relief and comfort from the local heat and soreness of these conditions than the application of diphemanil methylsulfate with hydrocortisone cream. The anhidrotic and analgesic properties of these preparations are ideal for their treatment. Nonirritating detergents must, of course, be used for cleansing the affected parts and the diapers.

Case 4.—In a seven-month-old girl, an extensive intertrigo and dermatitis involving the perineum, inner thighs, and buttocks developed after an attack of severe diarrhea. The lesions were so painful that bathing was difficult. Treatment consisting of cleansing with Aquaphor, in a water-in-oil base, drying and applying diphemanil methylsulfate with hydrocortisone cream after each diaper change resulted in the disappearance of the intertrigo and dermatitis. This treatment also proved successful in four other patients.

ATHLETE'S FOOT

Case 5.—A thirty-year-old housewife had trichophytosis of the right foot and "id" lesions on the right hand. The condition was refractory to treatment, and the patient had previously consulted several physicians, including a dermatologist. The lesions were extremely pruritic, and when vesicles formed the itching became intolerable. Potassium permanganate soaks and the application of half strength Whitfield's ointment, drying shake lotions, and Pragmatar cleared the lesions for months at a time, but exacerbations always occurred. Following intradermal tests with extracts of pathogenic fungi, a special treatment mixture was used as a vaccine. This adjunctive treatment resulted in much longer remissions. However, an exacerbation occurred in August, 1955. At that time, the vaccine and the usual measures were not used. Instead, treatment consisted of potassium permanganate soaks and, after drying, the application of diphemanil methylsulfate with hydrocortisone cream every four hours, both to the "id" lesions on the hand and to the moist pruritic eruption on the right foot. The "id" lesions disappeared. A slight dry lesion on the foot remains, which causes no discomfort and is gradually subsiding under continued treatment with soaks and the cream.

This case of trichophytosis was particularly severe and persistent. In other cases as well, and especially in those of the interdigital type, adjunctive treatment with diphemanil methylsulfate with hyrocortisone cream has resulted in more rapid improvement than treatment with other drying antipruritic lotions or ointments.

DERMATITIS MEDICAMENTOSA

Drug allergies as a cause of pruritus are extremely variable and of increasing importance. The lesions vary from the mildest itching or erythema, urticaria, and angioedema, to the most tenacious, severely in-

capacitating, and occasionally fatal eruptions. Early recognition and elimination are important, especially where drugs are suspected of aggravating a persistent dermatosis. Although certain drugs produce characteristic lesions which require different local treatment, itching, irritated, bullous eruptions should be treated at once with local applications of soothing remedies. Care must be exercised to exclude antipruritic remedies to which the patient is or may become sensitive, such as ointments or lotions containing benzocaine, phenol, camphor, or menthol.

Case 6.—A fifty-year-old male with a family history of eczema was first seen in August, 1954. He had a history of aspirin sensitivity and developed a pruritic angioedema followed by desquamation, which left the fingers raw and weeping and was associated with a peculiar taste in the mouth. Prior to this visit, he had an itching eruption on the right leg and on the dorsum of the left hand. A dermatologist diagnosed the condition as an infection, prescribed ointments the first week and pills the second, and gave the patient an injection of penicillin every other day for three injections. This treatment helped little, but the skin condition was not aggravated. Another injection of penicillin was given seven days later. An itching eruption developed on the scrotum, and an intensely itching and weeping eruption on both legs, both hands, and the axillae that necessitated treatment with packs wet with Burow's solution.

Injectible Chlor-Trimeton® Maleate was given daily for three or four days, and then every three days, with repeat action Chlor-Trimeton tablets orally on the days when an injection was not given. The acute dermatitis subsided, with some relief of the itching. At this stage, diphemanil methylsulfate cream was applied locally, and the patient noticed a marked decrease in the pruritus. The skin cleared within three weeks and there has been no recurrence. Aspirin is being avoided.

SEBORRHEA OF INTERTRIGINOUS TYPE

Seborrhea of the intertriginous type, involving the crural folds, axillae, umbilicus, retroauricular areas, and gluteal clefts, may be an acute process with oozing, crusting, and secondary bacterial infection, in which case soothing remedies are indicated. Because seborrheic skin areas are particularly susceptible to infection and eczematous changes, it is essential to recognize the seborrheic background. The condition may be complicated by an acquired sensitivity to contact allergens, such as nickel in white gold spectacle frames and medications. Food allergy may also contribute to the condition.

Case 7.—A sixteen-year-old girl had "blackheads and pimples" since the menarche. Her scalp contained whitish scales, and it and her skin had a tendency toward oiliness. Salicylic acid and sulfur lotions had been used on the face and tar soap on the scalp. Foods were not restricted in any way and, because of a tendency toward underweight, the patient ate large amounts of butter and sweet chocolate. She perspired profusely when working during the summer in a store basement with poor ventilation. The rapid onset of acute seborrhea involved the axillae, the backs of the ears, and the crural folds. There was also a mild blepharitis. The lesions became moist and were characterized by superficial, irregularly sized and shaped erythematous patches with oozing, crusting, and yellow scales. Examination revealed

extensive pyorrhea and tooth decay that necessitated many extractions and wearing of a partial denture.

The usual initial and undesirable application of compresses wet with Burow's solution or potassium permanganate was omitted. The patient wished to continue working so silver nitrate solution was not used because of discoloration. The acutely involved skin areas were cleansed with a soapless detergent, which the patient thereafter employed for bathing, and diphemanil methylsulfate with hydrocortisone cream was thoroughly applied. The patient was instructed to apply the cream three times daily. She was placed on a low-fat diet, excluding chocolate. The scalp was treated daily with applications of a lotion containing salicylic acid, mercury bichloride, glycerine, and alcohol, and weekly with vigorous applications of a liquid tar detergent. At the end of one week, the acute condition had subsided, leaving slight superficial patches of erythema. At the end of the second week, the intertriginous areas had cleared and the condition of the scalp and face had improved.

Acute seborrhea in two additional patients responded well to the same treatment.

LICHEN PLANUS

The beneficial effect of diphemanil methylsulfate with hydrocortisone cream was also seen in an acute case of lichen planus.

Case 8.—A thirty-year-old male, of nervous temperament, was first seen in September, 1955. He was suffering from overwork and anxiety associated with the launching of a new business. Although his general health was good, symmetrical lesions were present on the flexural surfaces of the forearms and wrists, and there was a circumscribed pruritic area on the dorsum of the penis. The lesions, flat, angular papules, were erythematous with a violaceous tinge. The patient's temperature was 100° F., and there was some malaise. Drug eruptions and syphilis were excluded. Intradermal tests with food extracts were negative, but he was cautioned to remain on a bland diet, and to avoid stimulants such as alcohol, coffee, and highly seasoned foods. The intense pruritus caused insomnia, which further increased the patient's fatigue and nervousness. Scratching seemed to spread the eruption. Since lichen planus frequently runs a self-limited course, initial therapy was directed toward controlling the intense itching. Diphemanil methylsulfate with hydrocortisone cream was applied and gently massaged into the affected areas as frequently as was necessary to control the itching. The response to this treatment was most gratifying to the patient, and the condition completely subsided.

MISCELLANEOUS

The pruritus of mild types of erythema multiforme may be relieved by the frequent local application of diphemanil methylsulfate with hydrocortisone cream. The intense itching from chicken pox, which is frequently followed by secondary infection due to scratching, can be controlled by antihistamines, such as tripelennamine hydrochloride or chlorprophenpyridamine maleate, along with generous local applications of diphemanil methylsulfate cream plain or, when infection is present, in combination with hydrocortisone.

SUMMARY

Diphemanil (Prantal) methylsulfate cream plain and with hydrocortisone has been used in the treatment of various skin diseases.

These anticholinergic creams controlled the pruritus more effectively than other local antipruritic measures. Reduction of the urge to scratch reduced the likelihood of secondary infection.

None of the patients treated with diphemanil methylsulfate cream, plain or with hydrocortisone, showed any side effects or toxic reactions.

The trial of these topical medications appears to be warranted in skin diseases where pruritus is present, regardless of their etiology.

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401 Marquette Bank Building

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PREVENTION OF ACUTE ALLERGIC AND FEBRILE REACTIONS TO BLOOD TRANSFUSIONS BY PROPHYLACTIC USE OF AN ANTIHISTAMINE PLUS AN ANTIPYRETIC

CHESTER C. WINTER, M.D., and GEORGE V. TAPLIN, M.D.
Los Angeles, California

A PREVIOUS study of acute allergic and febrile reactions to transfusions of whole blood[13] demonstrated that 10 mg of Chlorprophenpyridamine Maleate (Chlor-trimeton®) in each 500 ml unit reduces the incidence of acute allergic reactions to less than 1.0 per cent. However, this regimen failed to influence the rate of acute febrile reactions. In a carefully selected control group of 264 patients, the incidence of allergic and febrile reactions was 4.5 and 6.8 per cent, respectively. Furthermore, among individuals having a positive allergic background, acute allergic reactions occurred in 14.7 per cent, whereas the rate of febrile reactions was no higher than that found in individuals with a negative allergic history (6.9 per cent).

The two purposes of this report are: (1) to present data which show that both acute allergic and febrile reactions to the transfusion of whole blood may be almost eliminated by the prophylactic use of acetylsalicyclic acid orally plus the admixture of 10 mg of chlorprophenpyridamine to each unit of blood prior to its administration, and (2) to discuss the values of this prophylactic regimen to patients receiving blood transfusions, to the laboratory and professional personnel, and to the hospital administrator in respect to potential financial savings.

METHOD OF STUDY

Only carefully selected patients not receiving analgesic, hypnotic, anesthetic,[9] or antipyretic medication were included in this study. The blood used was collected in standard vacuum bottles containing ACD solution and was processed by techniques complying with National Blood Bank requirements. Pyrogen free, disposable, plastic transfusion sets were employed.

The data collected included the patient's past history of allergy (allergic rhinitis, allergic asthma, eczema, urticaria or a medical diagnosis of an allergic state) or reactions to previous drugs or transfusions, the amount of blood transfused, the dosage of chlorprophenpyridamine and acetylsalicylic acid given, the type and severity of subjective and objective reactions, and a record of the patient's temperatures immediately before and one and four hours after the onset of the transfusion. At the time the patient's temperature was taken, his skin was observed for allergic manifestations and he was questioned about symptoms of untoward reactions.

From the Departments of Surgery, Medicine, and Pathology, Veterans Administration Center, Los Angeles, California, and from the Departments of Surgery and Medicine, School of Medicine, University of California at Los Angeles, California.

The criteria for a febrile reaction were: (1) a definite chill, (2) at least a one degree F. elevation in oral temperature above 98.6 degrees F. or higher initial temperature with or without a chill, and (3) absence of a preceding febrile course or other condition which could account for chills or fever.

An allergic reaction included any of the following: urticaria or acute dermal erythema or eruptions, acute pruritus, edema or asthmatic symptoms.

If an immediate reaction occurred, the transfusion was stopped, a physician was called, and appropriate management was instituted. The Blood Bank was notified and routine investigations were made to determine the nature or cause of the reaction.

Each of 323 patients was given 0.65 gm of acetylsalicylic acid orally one hour before transfusion and every three hours thereafter as long as the blood was being administered; the minimal dosage was 1.30 gm. The contents of a 1 ml ampule (10 mg) of chlorprophenpyridamine was mixed with each 500 ml unit of blood. All patients were questioned about idiosyncrasy to salicylates.

RESULTS

A summary of our previous investigations of the frequency of acute allergic and febrile reactions to transfusion in untreated (control) groups and those given chlorprophenpyridamine is presented in Table I, along with results from this study of a similar group of 323 patients (Series E), each of whom received acetylsalicylic acid orally and chlorprophenpyridamine mixed with each unit of blood.

It has been shown that this antihistamine reduced the frequency of acute allergic reactions, particularly when it was mixed with the blood before transfusion (Series C and D). However, in our experience this drug had no beneficial effect on the acute febrile reactions,[12,13] contrary to some reports.[1,3,5,6,8,10] Actually an increase in febrile reactions was found among allergic individuals when it was added. However, among nonallergic persons, this occurred only when 10 mg of chlorprophenpyridamine was mixed with the blood.

Series E shows that a combined prophylactic regimen, consisting of acetylsalicylic acid to prevent febrile reactions and Chlortrimeton to prevent acute allergic reactions, is highly effective. The overall reaction rate to both febrile and allergic reactions totals less than 1.0 per cent, compared with 11.3 per cent among untreated controls.

Among the fifty-nine patients with a positive allergic background (Series E) the incidence of acute allergic reactions is only 1.6 per cent compared with 14.7 per cent in a similar group of untreated controls. In the 264 nonallergic cases in this same series, there were no allergic reactions whatsoever. The incidence of febrile reactions was much lower

TABLE I. EFFECT OF PROPHYLACTIC USE OF CHLOR-TRIMETON AND ACETYLSALICYLIC ACID ON THE INCIDENCE OF ACUTE ALLERGIC AND FEBRILE BLOOD TRANSFUSION REACTIONS IN ALLERGIC AND NONALLERGIC INDIVIDUALS

Series	No. Cases	Dosage in Mg. Chlor-trimeton	Reactions in Allergic Individuals							Reactions in Nonallergic Individuals							Reactions in Combined Allergic and Nonallergic Individuals						
			No. Cases	Allergic		Febrile		Total		No. Cases	Allergic		Febrile		Total		No. Cases	Allergic		Febrile		Total	
				No.	%	No.	%	No.	%		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
A	264	None (Controls)	61	9	14.7	4	6.5	13	21.0	203	3	1.4	14	6.9	17	8.3	264	12	4.5	18	6.8	30	11.3
B	131	4*	27	3	11.0	4	14.8	7	25.9	104	0	0	6	5.7	6	5.7	131	3	2.3	10	7.6	13	10.0
C	101	10*	38	3	7.8	6	15.7	9	23.6	63	0	0	3	4.7	3	4.7	101	3	3.0	9	9.0	12	12.0
D	213	10**	40	0	0	6	15.0	6	15.0	173	0	0	27	15.6	27	15.6	213	0	0	33	15.4	33	15.4
	350	10**	66	1	1.5					284	1	0.35					350	2	0.57				
E	323	10** Plus Acetylsalicylic acid	59	1	1.6	1	1.6	2	3.3	264	0	0	1	0.3	1	0.3	323	1	0.30	2	0.61	3	0.9

*Injected intravenously prior to transfusion.
**Mixed with each unit of blood.

among both allergic and nonallergic groups of individuals, when comparison is made with their control groups. No patients were found to have experienced significant reactions to either of the agents used.

COMMENTS

Analysis of the data accumulated from studying 905 carefully selected patients receiving transfusions with whole blood and given various types of prophylactic therapy designed to reduce the incidence of acute febrile and allergic reactions, compared with a control group of 264 similar patients, permits the following conclusions:

1. Allergic type reactions are about ten times more frequent in patients having a positive allergic history than among nonallergic individuals.

2. Acute febrile reactions occur with about equal frequency among allergic and nonallergic groups of individuals (6.8 per cent).

3. About one person in nine is likely to experience either a febrile or acute allergic reaction to transfusion, if no specific prophylactic measures are taken.

4. Only one nonallergic person in about seventy is likely to have an acute allergic transfusion reaction.

5. The prophylactic use of an antihistamine (Chlor-trimeton) is effective in preventing acute allergic reactions, particularly if a 10 mg dose is mixed with the blood prior to its administration.

6. This antihistamine alone has no prophylactic value for the reduction of acute febrile transfusion reactions.

7. A prophylactic regimen consisting of acetylsalicylic acid, 0.65 gm orally one hour before transfusion and repeated every three hours, plus 10 mg of chlorprophenpyridamine mixed with the blood, is effective in almost completely eliminating both types of acute transfusion reactions.

Although small intravenous doses of the antihistamine (2 to 4 mg) are adequate for the treatment of acute allergic transfusion reactions, such small doses are not sufficient for prophylactic purposes.[13] When the dose is increased to 10 mg some prophylactic effect is obtained. However, if this same dose is mixed with the blood to be administered, its value is enhanced. Our explanation for this finding is that with the latter technique, it is likely that adequate blood and/or tissue concentrations are maintained longer than when the drug is given rapidly by intravenous injection.

The failure of this antihistaminic agent to prevent febrile reactions to transfusion is not surprising in view of the reported causes[2,4,7] for such reactions, which seldom include those of allergic nature. Wilhelm et al[12] have found antihistaminics ineffective, both in preventing febrile reactions to transfusions and pyrogen-induced fever in rabbits. The significance of our finding an actual increase in febrile reactions among all allergic individuals and only the nonallergic persons in Series D, when Chlor-trime-

ton® was added, is not clear. In a previous report[13] it was found that intravenous chlorprophenpyridamine given alone did not produce a febrile response.

The maintenance of adequate blood salicylate levels during and for a few hours post-transfusion should prevent febrile reactions regardless of their cause, because the main action of the drug is on the temperature regulation centers in the brain. The effectiveness of salicylates in preventing acute febrile reactions to typhoid vaccine is well known. Also, it has been demonstrated by studies in rabbits[11] that the acute febrile response following mid-lethal doses of whole body x-irradiation may be eliminated by giving either sodium salicylate or aminopyrine thirty to sixty minutes before radiation exposure.

The results of this investigation (Series E) provide evidence that oral salicylate prophylaxis, with a single 0.65 gm dose of acetysalicylic acid, is effective. It is possible that two doses (0.65 gm each) given three hours before and again one hour prior to transfusion might be even more effective because this regimen would be more likely to provide adequate salicylate blood levels during and just after the average transfusion.

From the results of this study it seems likely that a wider application of this dual prophylactic regimen to patients receiving transfusions in a large hospital, could provide several added benefits, other than the primary one of sparing patients the discomfort of acute febrile and allergic type reactions. At present only a rare acute reaction to transfusion is proved to be caused by hemolytic factors. Thus, a large reduction in non-hemolytic reactions not only will reduce the number of unnecessary blood samples returned to the laboratory for retyping and other time-consuming procedures, but will also tend to pinpoint true immunologic reactions. Furthermore, large supplies of partially used samples of blood from patients having non-hemolytic reactions during transfusion are now discarded. Therefore, in hospitals having an active transfusion service, using 500 units of blood or more per month, a twelve-fold reduction in acute reactions could result in a sizable saving in time of medical, administrative, and laboratory personnel, and in direct costs of blood supplies amounting to several thousands of dollars per year.

It is recommended that a routine prophylactic program be limited initially to medical and surgical ward patients receiving not more than 20 mg chlorprophenpyridamine per six hour period, and extended to patients undergoing major surgical procedures on an investigative basis only, until such a routine procedure has been proved to be entirely safe.

SUMMARY

The high incidence of both acute febrile and allergic reactions to the transfusion of whole blood (11.3 per cent) may be reduced to less than 1.0 per cent by the prophylactic use of an antipyretic (acetylsalicylic acid)

orally plus the admixture of an antihistamine (Chlorprophenpyridamine maleate Chlor-trimeton) to each unit of blood prior to its administration. This antihistamine is far more effective when mixed with the blood and given slowly than when administered separately by intravenous injection just before transfusion. Alone, it is not beneficial in preventing acute febrile transfusion reactions.

The potential values of adopting a routine prophylactic regimen to reduce the high incidence of both acute febrile and allergic blood transfusion reactions are discussed in respect to the patients concerned, the saving of administrative, medical, and technical personnel time, and the reduction of direct costs for blood supplies.

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Wadsworth V.A. Hospital
Wilshire & Sawtelle Boulevards
(Dr. Winter)

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THE EFFECT OF CUPRIPORPHYRIN ON ANTIGENICITY AND PYROGENICITY OF INFLUENZA VIRUS VACCINE

MARK D. FREEMAN, HENRY T. STANTON, JR., ROBERT D. BARNARD and BENJAMIN GOLDMAN

Mount Vernon, New York

IMPORTANT generalizations have resulted from the demonstration that polyelectrolytes modify virus behavior[18,27] and that macromolecular substances, depending on their charge, direction and dispersion may modify immune reactions. The latter fact is fully demonstrated, if still unexplained, by the studies of Glynn et al[17] on dextrans. In specific virology some knowledge of macromolecular effects has also accumulated. Macrocations generally reduce virus infectivity as well as antigenicity[11,24] by mutually antagonistic colloid action. Macroanions, on the other hand, appear to limit virus infectivity by competitive inhibition, through chemical structural similarity and an ability to form dissociable linkages with the phospholipid (electropositive) cell receptors. While the effect of macroanions on virus antigenicity has not been thoroughly explored, it is presumed that there would be no interference with the latter; animal viruses are themselves macroanions and at least one demonstrated adjuvant for a virus vaccine, phosphorylated hesperidin[28] is a macroanionic material with defined heparinoid and antidepolymerase properties.[8,21,26] The "antihyaluronidase" phase of this last property has been invoked to explain the adjuvant action of phosphorylated hesperidin to subcutaneously or intramuscularly administered corticotrophin,[12] it being presumed that the induced curtailment of "spreading effect" would make for longer reposition of the prime material in a tissue depot. The addition of "antihyaluronidase" to influenza vaccines had the same underlying theory;[5] one that must necessarily be questioned on the basis of the present report.

The metalloporphyrins also are macroanionic in aqueous dispersion and yield marked antithrombic and antihyaluronidase effects. These effects were first noticed in relation to ferriprotoporphyrinate.[1,31] Later the water-soluble "chlorophyllins" of commerce were shown to possess pronounced antidepolymerase activity;[2] about fifty times that of equivalent concentrations of phosphorylated hesperidins.[3] Competitive inhibition of virus hemagglutination is an expression of antidepolymerase activity.[4] The chlorophyllins, which are cuprimonovinyldihydroporphyrins, have shown inhibitory effects against the classic hemagglutinating viruses (influenza, mumps, Newcastle)[14] and against infectivity by certain neurotropic, dermotropic and bacterial viruses as well.[5] In addition it has been found that all properties of the chlorophyllins held to be contingent on

From the Lindsay Laboratories, Brooklyn, and the Research Department of the Rystan Company, Mount Vernon, New York.

TABLE I. THE EFFECT OF INFLUENZA VIRUS VACCINE INTRAVENOUSLY ON THE TEMPERATURE AND ANTIBODY RESPONSE OF RABBITS

1st Series Rabbits	Morning-Evening Control		Pre-Administration	Post 1 Hr.	2 Hr.	1 Hr. Rise	2 Hr.	P-Control	AHT*
1	101.0	102.4	100.0	103.9	104.0	3.1	3.2	101.0	1:4
2	101.0	101.3	101.0	103.0	103.0	2.0	2.9	dead	
3	100.0	100.0	98.8	104.0	103.2	5.2	4.4	101.2	1:4
Averages-Control (vaccine alone) series						3.4	3.5	1.1	
4	99.9	100.0	102.0	103.5	103.8	1.5	1.8	100.2	1:325
5	101.5	102.0	101.9	102.0	102.2	.1	.3	100.2	1:32w
6	102.0	103.1	100.2	102.1	104.2	1.9	4.0	101.0	1:16
Averages vaccine in 0.5% chlorophyllin						1.2	2.0	1:4	
7	101.6	102.3	103.0	104.8	103.0	1.8	.0	dead	
8	101.0	103.0	101.7	102.5	103.1	.8	1.4	dead	
Averages vaccine plus sodium phosphomolybdate 0.5%									

*Antihemagglutination titer of serum 10 days post-immunization.

their macroanionic structure are shared, quantitatively at least, by a series of synthetic, water-soluble azaporphyrin dyes, the phthalocyanin polysulfonates. Because of its marked similarity, chemically and pharmacologically (particularly in its relative absence of toxicity),[13] to the chlorophyllins, the cupriphthalocyanin trisulfonate, "Pontamine" has been compared with the plant-derived porphyrin as an adjuvant to mixed influenza vaccine. Practical considerations for choosing the latter were: (1) its extensive use in humans where it is known to exert (like any formalin-inactivated virus may) an "aggressin" effect; (2) ability to demonstrate this effect by pyrogenicity response in rabbits;[9] and (3) suitability of that animal for the rough quantitation of the immunologic response to influenza virus vaccine.

EXPERIMENTAL RESULTS

Six to eight week-old female rabbits were each injected intravenously with 0.5 ml of mixed influenza vaccine (Lederle) diluted 1:lv/v with pyrogen-free pH 7.4 buffered physiologic saline alone (control groups) or with a solution of the metallomacroanion in 1 per cent concentration. The adjuvant therefore existed in the experimental vaccines in 0.5 per cent concentrations. A preliminary experiment (Table I) served to indicate that phosphomolybdates, while blocking the usual pyrogen response to the vaccine in which they were incorporated, resulted in the death of the injected animals. While this could have been due to inherent toxicity of the particular (technical) grade of phosphomolybdate used, the ensuing results with chlorophyllin dictated our concentration on the utility of the soluble cupriporphyrins, particularly when comparative antibody responses were quantitated.

Determination of immunization was made on serums obtained twenty-four hours postprandially. The suppression of hemagglutination of a 2 per cent pH 7.4 buffered physiologic saline suspension of human, O Rh_o

TABLE II. COMPARISON OF ADJUVANT EFFECTS OF A CUPRIPORPHYRIN FROM NATURALLY DERIVED AND SYNTHETIC SOURCE

Adjuvant	Temperatures** °F				AHT*
	Before Administration	After 2 Hrs.	6 Hrs.	24 Hrs.	
None (saline)	101.1	103.7	102.5	100.9	1:4
	Pyrogenicity	2.6	1.4	—0.2	1:8
					1:8
					1:32
				Average	1:13
Chlorophyllin 0.5%	103.2	104.2	103.9	102.2	1:32
		1.0	.7	—1.0	1:32
					1:64
					1:32
				Average	1:40
Phthalocyanine .5%	102.4	104.5	102.7		1:16
		2.1	.3	—1.3	1:64
					1:32
					1:16
				Average	1:32

*Antihemagglutination titer of serum 8 days post-immunization.
**Averages of 4 animals in each group.

cells by a sample of the particular lot of influenza vaccine used in the immunizations, diluted to give a "standard" titer of 1:512, was measured by incorporating geometrically progressive dilutions of the rabbit serum under test. The lowest concentration of the latter reducing this standard titer by three tubes is expressed as the antihemagglutination titer (AHT) of the serum in Tables I and II which also records the interval temperatures in the corresponding rabbit after the immunizing injection.*

A second series of pyrogenicity responses and antibody titers, in which chlorophyllin adjuvancy was again compared with untreated vaccine, on the one hand, and with Pontamine, on the other, has its pertinent data recorded in Table II, except that a six-hour recording was substituted for the one-hour recording of temperature for the first series. It is evident that either chlorophyllin or Pontamine limit the pyrogen response to influenza vaccine while at the same time they permit this material to function antigenically.**

*Previous experiments in this laboratory show that non-immune rabbit serum, undiluted, has about the same effect on the human erythrocyte-influenza vaccine system as the 1:4 dilution of the immune serum from vaccine-saline immunized animals and the 1:32 dilution from those in which chlorophyllin adjuvant was used. No correction for normal "inhibitor" is made for the listed titers in either groups because the data are purely comparative, i.e., the difference between adjuvanted and plain vaccine is intrinsically significant, and such effect would be negligible in any case. However, it should not be construed from the tabulated AHT's that the antibody content of vaccine-saline immunized animal serum is "four times" that of non-immunized animals, or that the vaccine-chlorophyllin has "thirty-two times" the antibody content. Such a calculation would ignore the progressively diminishing conglutinin effect of the weaker dilutions of serum.

**In addition to the titer differences noted between untreated and adjuvanted virus vaccine immune serums, there is also a difference in the "avidity" of the hemagglutination phenomenon, that being conducted in the presence of the latter being much less avid. This difference cannot easily be quantitated.

DISCUSSION

Antiviral effects of competitive hyaluronidase inhibitors have been well known.[2,14,16,18,19,20,22,25] These materials are macroanionic compounds which have been useful adjuvants to virus vaccines,[16] as well as to certain endocrine preparations.[6,12,13] It has been assumed that they prevent depolymerization of the hyaluronic acid of the tissues around the injected area and thus make for slower sustained release; a repository or "depot" effect. However, such a mechanism for hyaluronidase would not operate adjuvantly on intravenous administration, as in the present case, nor in the case of alkali hematinate potentiation of intravenous insulin.[6] Hematin, like chlorophyllin and other metalloporphyrins,[31] is a potent antihyaluronidase.

Cortisone reputedly exerts its antipyretic and antiphlogistic effects on the basis of hyaluronidase inhibition[19] but another cationic material, aureomycin which is not antihyaluronidase, curtails influenza vaccine pyrogenicity in rabbits.[29]

Our working hypothesis on the mechanism of pyrogenicity abolition of influenza virus without loss of antigenicity actually follows from the studies of Bennett, Wagner and LeQuire[10] who evolved the pyrogen determination method herein employed. They found a twelve-day refractoriness after influenza virus administration to reinjection of the same type of virus. They consider the first injection to occupy all available cell receptors for virus and that further virus attachment cannot occur until new receptors can regenerate. We consider such receptors to be positively charged, i.e., cationic cholesterol lecithitides of the cell wall, and that macroanionic hyaluronidase inhibitors can priorly occupy such receptors to the exclusion of virus occupation. A similar explanation of the abolition of Shope fibroma virus infectivity by a hyaluronic acid analogue was recently advanced by Pearce and LaSorte.[25]

The search for an "antibiotic" of direct utility toward virus disease has proved unavailing. Present trends are toward active immunization with killed or attenuated viruses. It is evident that these may still attach to cell receptors, and if pyrogenicity response is any indication, that they are not metabolically inert. The fact that it may be possible to prevent this pyrogen response without disturbing the defined goal of virus vaccine administration—an active immune response—is encouraging.

CONCLUSIONS

Three species of metallomacroanionic hyaluronidase inhibitors were found to limit the pyrogen response of rabbits to the intravenous injection of influenza virus vaccine. The immunity response to this vaccination was enhanced by the incorporation into the vaccine of two metalloporphyrins, sodium cuprichlorophyllinate and sodium cupriphthalocyanin sulfonate. Sodium phosphomolybdate also curtailed the pyrogen response but

proved too toxic in the concentration employed, the rabbits dying before an evaluation of antibody response could be made.

The hyaluronidase inhibitors are believed to preoccupy the cell receptors to which virus ordinarily attaches and thus to prevent the attachment of the latter.

Incorporation of competitive hyaluronidase inhibitors for virus vaccines may prove to be a useful expedient.

SUMMARY

To test the theory that macroanionic hyaluronidase inhibitors were competitively "antiviral" and would not interfere with antibody production by a virus vaccine, rabbits were given killed influenza virus incorporating hyaluronidase inhibitors of this class. Sodium phosphomolybdate 0.5 per cent, sodium cuprichlorophyllin 0.5 per cent and sodium cupriphthalocyanin sulfonate 0.5 per cent were each added to portions of influenza virus vaccine and each antihyaluronidase treated portion tested for pyrogenicity on intravenous injection to rabbits. The pyrogen response was less than that in a control group given influenza virus vaccine alone. The group receiving the phosphomolybdate vaccine did not survive but influenza antibody titer, determined by hemagglutination inhibition, was higher in the other two experimental groups than in the controls. It is concluded that the addition of a hyaluronidase inhibitor to virus vaccines might be a useful expedient to limit pyrogenicity and enhance antibody production ensuing from administration of such vaccines.

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7 North Macqueston Parkway
Mount Vernon, New York (Henry T. Stanton)
73 Hanson Place
Brooklyn, N. Y. (Mark D. Freeman)

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NETHERLANDS SOCIETY OF ALLERGY

In May, 1958, the Netherlands Association of Allergy will sponsor an International Course on Occupational Allergy to be held in the Netherlands Universities' Foundation for International Co-operation, Noordeinde Palace, The Hague. The program, which will be in charge of well-known Dutch and other European allergists, will include lectures on allergy among the various occupations: nurses, bakers, the cosmetics industry, et cetera, accompanied by demonstrations of allergic examinations and allergic patients. Side excursions to see the flowers, vegetables, and other points of interest will be included.

NEUROPATHIC MANIFESTATIONS IN INFANTS AND CHILDREN AS A RESULT OF ANAPHYLACTIC REACTIONS TO FOODS CONTAINED IN THEIR DIETARY

(Historical Document)

W. RAY SHANNON, M.D.
Saint Paul, Minnesota

The close association of the exudative and neuropathic diatheses suggests a causal relationship. The frequent anaphylactic nature of the former[1] would seem to point toward a similar cause in the latter. It is my purpose in this paper to discuss certain nervous manifestations in infants and children from the standpoint of anaphylactic cause.

It is hardly necessary to call attention to the frequent occurrence of the exudative and neuropathic diathese in the same individual. All observers recognize the common association. However, it seems to have been generally held that this relationship is nothing more than accidental. Czerny considered it so.[2] He felt that the almost universal presence of the neuropathic diathesis in one or both parents of children with the exudative diathesis led, as a natural result, to the neurotic child. The degree to which the infant was affected by this nervous environment determined, to a certain extent, the obstinacy and severity of the exudative manifestations. Pfaundler[3] stated that the sneezing in coryza, pertussoid in bronchitis, asthma in bronchiolitis, severe colic in enteritis, et cetera, were dependent, to a certain degree, on the coexistence of a neuropathic diathesis along with the exudative diathesis.

This common association, together with the fact that frequently in the same individual the symptoms of one, and again the symptoms of the other diathesis, will seem to predominate, led me to the opinion that not infrequently the symptoms of both conditions might be due to the same underlying factor. Inquiry revealed the fact that often nervous patients have a history, either personal or familial, of exudative disturbances, and the frequent anaphylactic basis for the exudative phenomena suggested that the nervous symptoms might also be due to this cause. Therefore, this investigation was undertaken to see if this might not be the case clinically.

The cases presented are of three types: first, the type in which the symptoms of both diatheses were plainly present; second, the type in which the present symptoms were nervous but in which there was a definite exudative history; and third, the type in which the symptoms were those of the neuropathic diathesis without a history of frank exudative phenomena preceding. With one case experimentation was possible.

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REPORT OF CASES

Case 1.—A girl, five years of age, presented an urticarial eruption and asthma. The mother stated that the patient was very high-strung and nervous. There was a history of hay fever in the father and of eczema in several cousins. Skin tests revealed positive erythematous reactions to several foods of which the patient was eating a great deal. Removal of the offending foods from the patient's diet resulted in early relief from nervous manifestations and from the urticaria and asthma.

Case 2.—A boy, two years and eight months of age, had a history of a very itchy skin eruption, apparently of an urticarial nature, rather loose stools, and extreme nervousness. Whereas he normally slept well at night and took a nap during the daytime, of late he would not sleep at all during the day and very poorly at night. He was very irritable.

Cutaneous tests showed erythematous reactions to a number of foods he was eating. Modification of the diet and eliminating as much as possible the foods to which he was sensitive resulted in complete disappearance of the skin and nervous symptoms in two weeks' time. The child became himself again, was not irritable, and slept well at night, and took a long nap during the daytime.

Case 3.—A boy, four years old, had a history of eczema and asthma. He was extremely high-strung and very nervous. His appetite was rather poor and he was very finicky about what he ate. He slept poorly at night. The mother complained that he could not sit still and that he was very hard to manage. Skin tests revealed erythematous reactions to a large number of foods and to a number of animal emanations. The diet was regulated and he was instructed to stay away from the animals to whose proteins he was sensitive. Relief from asthmatic symptoms had occurred nine days later and the eczema had improved considerably. Eighteen days after the tests were performed he was still free from asthma and there was only a slight chapping of the cheeks. The nervousness had improved greatly. His general restlessness was gone. He slept better at night and slept well during the daytime. His appetite was very good and he gained two and one-half pounds in weight. At the present time, one month after the institution of treatment, the improvement has continued.

Case 4.—A girl, twenty-eight months old, was brought in because of an urticarial eruption and nervousness. Local treatment for the urticaria only was advised. Three weeks later she was brought back. The skin condition seemed improved, but the mother stated that the child was very irritable. She was unruly, peevish, ate poorly, and did not sleep well.

Skin tests revealed positive reactions to a number of foods the patient was eating in rather large quantity. These included egg and wheat. A diet was advised eliminating as nearly as possible the offending foods. Improvement was noted one week later but the mother said that she had been giving store cookies containing both egg and wheat to the patient. These were discontinued and after another interval of two weeks there was considerable improvement, especially in the nervousness. The mother asserted that the child "could be reasoned with." On one occasion the patient had been given spaghetti and tomatoes for her evening meal and both skin and nervous symptoms were much worse thereafter. At the present time, six weeks after the tests were performed, the nervousness is gone and the skin is clear.

Case 5.—A boy, twelve years of age, had been subject to eczema when an infant, to hives as he grew older, and still later to attacks of asthma. All these symptoms had been absent for a number of years, with the exception that he had had an attack of urticaria a few months previous to the first observation. The present com-

plaint was that of fever for the past few days, extreme nervousness, constant stuffiness in nose, occasional attacks of vomiting, and frequent headaches. He was extremely introspective, cried easily, was very irritable, and was constantly "out of sorts."

A period of hospital study revealed a chronic inflammatory condition of the nasal sinuses. Treatment of this condition resulted in relief from the headaches and disappearance of the fever and nasal obstruction. However, the nervousness remained.

Skin tests revealed sensitization to several foods, a number of pollens, although the parents had never suspected the presence of hay fever, and to horse dandruff and dog hair. A diet was advised and the patient instructed to stay away from dogs and horses.

Prompt improvement in the nervous symptoms resulted and this has been permanent over a period of seven months, except for a single attack of vomiting.

Case 6.—A boy, eight years old, was brought in because he was extremely irritable, did not eat well, was cruel to his playmates, and was unable to apply himself at school. As a result of the latter condition, he spent two years in the first grade.

He had been perfectly normal, except that he had had head colds almost from birth until he was four years old. At that time he had had a series of convulsions without ascribable cause. He was studied by nerve specialists, internists, and eye, ear, nose and throat men, the final impression of the physician in charge being that the convulsions were due to a "food poisoning" of some kind. There had been no convulsions since that time.

A complete physical examination, including blood, spinal fluid and urine studies, Wassermann test, Pirquet test, failed to reveal anything abnormal. There was no family history of sensitization phenomena. Cutaneous tests revealed positive erythematous reactions to wheat, spinach, egg white, whole egg, pear, orange, pea, beef, and figs. Questionable reactions were obtained to lactalbumin and banana. The patient was instructed to eat no wheat cereal or pastries, spinach, egg white, pea, orange, pear, beef, figs, or banana. He was to eat rye bread.

Nothing was heard from him for six weeks, when the mother reported that the boy had been a different child from the time he had gone on the diet. His irritability was lessened; he was no longer cruel to his playmates; he was doing well in school, and his appetite was good. When heard from again three months after the diet was instituted the improvement had continued and he had made his grade in school without difficulty.

Case 7.—A boy, nine years of age, suffered from extreme nervousness and attacks of vomiting. The periodic attacks ordinarily came on infrequently, not oftener than once a month. Usually he would vomit but once but was always indisposed for several days thereafter. Between the attacks he was irritable, slept poorly, and was very finicky about what he ate. He was extremely highstrung. For the past two weeks he had been vomiting every third day, would eat almost nothing between attacks, and was so irritable that he was a problem to his parents.

His past history was negative for protein sensitization, with the possible exception that he had been a difficult feeding case from three to fourteen months of age. From that time until four or five years he had been perfectly well. The vomiting attacks began at that time. He always coughed when he caught cold. When first seen he had been under treatment for some time for nasal sinusitis.

The immediate family history was negative for asthma, hay fever, urticaria, or eczema. One sister had had similar vomiting attacks at one time in her life. One cousin could not eat eggs because they poisoned her. The paternal grandfather had had attacks of difficult breathing in his old age which apparently resembled asthmatic attacks.

Physical examination revealed nothing except that the patient was somewhat pale and undernourished. He was, therefore, tested with foods of his dietary. Positive erythematous reactions were obtained to wheat leucosin, wheat gliadin, wheat proteose, pea, pineapple, potato, and navy bean. The reactions to fig, brazil nut and rye were questionable.

The patient was instructed to eat no peas, navy beans, string beans, lima beans, pineapple, figs or brazil nuts. He was to eat potato no more than four times weekly, and no wheat cereal or pastries made from wheat flour. Rye bread only was to be eaten, with the exception of a small amount of white bread toast. Arrowroot or cornstarch were to be used for thickening gravies.

Improvement was almost immediate. There were no more vomiting spells. His appetite became ravenous. The mother said that she could not "fill him up." All signs of nervous irritability ceased very shortly after the diet was instituted. He began to sleep all night and to waken refreshed, which he did not do before. During the following month his class standing rose from thirteenth, where it had been constantly for five months past, to eighth, without any conscious effort on his part. At present, two and a half months after the diet was prescribed, there has been no return of either nervousness or vomiting.

Case 8.—Girl, aged five months suffered from undernutrition. The family history was unfortunate. The child was illegitimate and nothing was known of the father. The mother was committed to an institution for the feeble-minded after deserting the infant.

The baby was partially breast fed for two months and since that time had been fed on milk mixtures. Cream of wheat was added to the infant's diet and seven days thereafter it was noticed that the child was extremely restless. There was constant movement of the arms and legs, with jerky movements of the entire body. The infant constantly turned and twisted in her crib. She cried incessantly day and night and slept but little throughout the twenty-four hours.

No cause was found on physical examination. There was no evidence of infection; the skin was clear; and the stools normal. The symptoms were attributed to a nervous diathesis dependent on the questionable heritage, and bromides were prescribed. These afforded marked relief and were discontinued after a short time. The infant immediately reverted to her former condition. Again bromides were given and the condition was controlled for a considerable period. However, they gradually lost their effect and about three months later (January, 1922), the patient's condition was as bad as it had been before the bromides were started.

On January 25 cutaneous tests were performed with several cereals, vegetables and cow's milk. Positive reactions were obtained to wheat leucosin, proteose and globulin. All of the rest were negative. Wheat cereal was discontinued and oatmeal was substituted. The bromid was discontinued.

One week later the child's disposition had changed remarkably so that it was noticed by all who came in contact with her. She slept all night and was playful and happy during the daytime. She cried but little. She had gained seven and one-half ounces during a period of four days.

On February 5 cream of wheat was again added instead of the oatmeal. Twelve hours later a return of the old irritability was noticeable. She was very restless all the next day, turning, twisting, and throwing herself about in her crib. That night she slept less well and cried a part of the night. The symptoms continued throughout the seventh and that night she cried all night. On February 8 the cream of wheat was discontinued and the oatmeal again substituted. Improvement was prompt and by the night of the thirteenth the patient slept all night. By February 17 she was happy and playful, as she was during the first experimental period. Since that time she has remained so.

Of the cases cited the first four presented skin eruptions. The natural explanation of the nervousness in these cases is that it is the reasonable accompaniment of the skin irritation. However, in all but Case 1 the nervous manifestations were out of all proportion to the severity of the skin lesions. Nevertheless, the nervous disturbances cleared up under specific therapy directed at the cutaneous and, in some cases, the respiratory symptoms. Furthermore, in Case 4, the skin lesions were better at the time of the second visit than they were when the patient was first seen, whereas the nervousness was much worse.

Case 5 presented no skin eruption to account for the nervousness. True, there was a chronic focus of infection in the nasal sinuses which might, in a measure, have accounted for at least a part of it. However, under treatment this focus cleared up without improvement of the nervous symptoms, and it was not until the unexpected, wide-spread sensitization was found and treatment directed against this factor was instituted that improvement in his neuropathic tendencies occurred. Whether the nervous symptoms were due mainly to food, pollen or animal sensitization is purely conjectural and immaterial since we should expect that they might be the result of all these anaphylactic causes.

Cases 6 and 7 were purely nervous cases. While an anaphylactic basis for Case 7 was suggested by the history of periodic attacks of vomiting,[4] such attacks are also described as being one of the manifestations of the neuropathic diathesis. The results obtained in each case were so definite as to leave no doubt that the symptoms complained of were due to anaphylactic reactions to foods contained in the diets of the patients. In Case 8 it was possible to relieve or bring on the nervous symptoms by removing from or adding to the patient's diet the food to which she was sensitive.

That anaphylaxis might be responsible for nervousness in man through irritation of the nervous system is sound theory. Anaphylaxis is fundamentally a nervous phenomenon. Besredka emphasized this fact and founded his method for the production of shock on this principle.[5] The symptoms as seen in the experimental animal support his contention. The extreme irritability and restlessness noted immediately on injection, the scratching of the muzzle, frequently the sneezing, the dyspnea due to bronchiolar spasm, later the sudden hopping movements, and finally the convulsion itself are indisputable evidence that the nervous system is profoundly affected.

In man nervous manifestations are inseparably associated with anaphylactic phenomena. The extreme nervousness noted in individuals accompanying attacks of asthma, hay fever, urticaria, and eczema are common knowledge. Often these attacks have been attributed to nervousness, the patient not recognizing the fact that, perhaps, both the nervousness and the attack are ascribable to the same cause.

The effects of drugs on anaphylactic phenomena are further support

for the nervous origin of the symptoms. Epinephrine, so valuable in asthma and urticaria, atropine and even morphine are notable drugs that act on the nervous system. Even general anesthetics greatly modify the character of an anaphylactic shock.

There is, then, an abnormal condition occurring very commonly in infants and children which would seem to give rise fundamentally to irritative phenomena of the nervous system. Is it not reasonable that such a phenomenon might give rise to all manner of symptoms ascribable to nervous origin within the body? Might it not be responsible for any of the symptoms frequently placed under the caption of the neuropathic diathesis? In fact, is there any limit within the field of the so-called functional nervous diseases beyond which such a cause could not be operative?

SUMMARY

Eight cases showing marked evidences of the presence of the so-called neuropathic diathesis in infants and children have been presented. In four of these definite evidence of the exudative diathesis was also present, while in still another there was a positive history of such a condition in the past. The remaining three cases gave no evidence suggestive of the presence of an exudative diathesis. All the patients showed definite relief from the nervous symptoms on the institution of specific therapy directed at the proteins to which they were sensitive. In all but one of the eight cases the proteins concerned were those of foods contained in the dietaries of the patients. In one case animal emanations or pollen proteins might have played a part. In one case the nervous symptoms could be relieved or brought on by the exclusion from or the addition to the diet of the food to which the patient was sensitive. Evidence is presented showing that anaphylaxis is a sound, theoretic basis for the explanation of many of the symptoms of the so-called neuropathic diathesis.

CONCLUSIONS

1. Many of the symptoms of the neuropathic diathesis in infants and children are not infrequently the result of irritation of the nervous system resulting from anaphylactic reactions to food proteins to which the patient has become sensitized. It is recognized that any protein to which the patient is sensitive might also be causative.

2. The frequent association of the exudative and neuropathic diathesis in infancy and childhood is, therefore, something more than accidental, the presence of each frequently being attributable to the same cause.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

TWELFTH ANNUAL CONGRESS

The Instructional Course and the General Session of the Twelfth Annual Congress differ markedly in pattern from previous years.

In broad outline, the Instructional Course will begin on Sunday, April 15, 1956, rather than on Monday morning. The Chairman, Dr. Morris Kaplan, and the Co-Chairman, Dr. M. Murray Peshkin, envisaged a new type of postgraduate program. There are fewer papers, but the subjects discussed are given both overall theoretical and more detailed practical importance. Following several papers in each morning and afternoon session, there is a "treatment conference" of the panel type with adequate provision for participation by the physicians attending the course.

Another departure from tradition scheduled for Monday evening, April 16, is a "Beer and Buffet supper" for the student participants. The instructors, officers of the College, and chairmen of the College committees will be present to amplify the subject matter of the Instructional Course and answer questions as well concerning the aims, purposes and activities of The American College of Allergists.

The method of registration and the purposes of the Instructional Course also vary from previous practice. A fee of $45 has been set for the full three-day session. For students attending the buffet supper, which is optional, the charge will be $50. Physicians may attend the second and third days, for which the registration fee is $30, or the last or any single day for a fee of $15. Another departure from tradition affects all classes of membership in The American College of Allergists. For these, any member in good standing may attend the entire course for a registration fee of $25. Any Fellow who wishes to attend any one morning or any one afternoon session of the Instructional Course will be issued a "Courtesy Card." (Sorry! Only one to a customer!)

On Tuesday afternoon, registration for the general session will begin. Scheduled for the evening will be a cocktail party under the auspices of the New York Allergy Society.

The general session will begin on Wednesday morning. There will be no evening sessions except for the Society for Mycological Investigation and the Medical Writers' Workshop, both scheduled concurrently for 8 p.m. on Wednesday. There will be no banquet, but the cocktail party sponsored by the Schering Corporation is scheduled for 6:30 p.m., Thursday evening.

The sections in Dermatology, Otolaryngology and Pediatrics will run concurrently on Friday morning, with Psychosomatic Medicine set for Friday afternoon. The Pediatrics section luncheon will feature Dr. Bela Schick as guest speaker. All registrants may attend. On Thursday afternoon, the guest speaker will be Professor M. G. Sevag of the University of Pennsylvania, whose subject will be "A New Theory of Allergic Phenomena."

For the general session, the speakers have been given three choices: they may take all of the time allotted, they may give some of their allotted time to a discussor of their own choice, or they may have open discussion from the floor.

Students, Fellows, instructors and officers of the College have a free weekend to journey to New York for the meeting, and another weekend to return home, or either or both. Weekends are available for entertainment in New York, and evenings have been left free for the varied attractions for which the city is famous.

The program chairmen and the officers of the College hope that you will agree that the 1956 meeting has offered the best instructional course, general session, and section programs the College has ever presented.

See you in New York in April!

—E.A.B.

NEWS OF MEMBERS

Dr. Bret Ratner of New York City was honored by the Section on Allergy of the American Academy of Pediatrics at a meeting held in Chicago, Illinois, October 3, 1955. Dr. Jerome Glaser of Rochester, New York, chairman of the Section, presented Dr. Ratner with a scroll which read as follows:

"By unanimous vote of the Section on Allergy of the American Academy of Pediatrics assembled in Chicago at the Twenty-Third annual meeting of the academy, this scroll is awarded to Bret Ratner, M.D., as an expression of gratitude and appreciation for his untiring services in advancing pediatric allergy: As a pioneer investigator and teacher; as organizer of the Section of Allergy and as its first chairman; and for his successful efforts in obtaining recognition by certification for pediatric allergists in the sub-specialty of pediatric allergy."

* * *

Wilkes College, Wilkes-Barre, Pennsylvania, has established within the Department of Biology a research laboratory devoted to the study of experimental hyposensitivity and related immunologic studies. Sheldon G. Cohen, M.D., is serving as director of the research project.

Progress in Allergy

GEL DIFFUSION

A Quasi-critical Review of Recent Literature

R. P. WODEHOUSE, Ph.D.

Pearl River, New York

The earlier literature on gel diffusion has been well covered by Oudin,[48] who has also been one of the major contributors to its modern development, which may be said to have started with the publication of his method of immunochemical analysis by specific precipitation in a gelatinous medium in 1946. His review, entitled "Specific Precipitation in Gels and its Application to Immunochemical Analysis," traces the development of this technique from its beginning with Bechhold in 1905 to the time of Oudin's publication in 1952. Since that time other less complete but important reviews have followed. These are Becker,[4] Ouchterlony,[47] Wodehouse,[68] Munoz.[42] Since these extend the coverage well into 1953, it is proposed to take this as the starting date for this review.

For the benefit of those who are not familiar with the principles of gel diffusion a short description of them follows.

Gel diffusion is a term used to designate antigen-antibody reactions taking place in semi-solid media. Other expressions commonly used are: serum-agar precipitation, specific precipitation in gels, et cetera. The immunologic principles involved are those of the ordinary precipitin reaction, while their kinetics are those of diffusion.

Ordinarily where specific precipitates are formed they fall to the bottom of the vessel or, in the ring test, remain at the interphase boundary between the two reactants; with gel diffusion techniques the precipitates form in a gelatinous medium where they remain, or else they drift slowly away from one or the other reactant sources by dissolving in its excess and reprecipitating in the region of optimal proportions in response to changing diffusion gradients. At all times the precipitates remain visible so that their patterns may be examined and their progression recorded, giving both immunologic and kinetic information about their reactants.

There are two basic methods by which this is done, single diffusion and double diffusion. The former is generally used for quantitative studies and the latter for qualitative. For quantitative estimation of antigen the homologous antiserum is combined with melted agar, poured into small test tubes and allowed to congeal, then a series of dilutions of the antigenic extract are overlaid and allowed to diffuse into the serum-agar mixture. As the antigen reaches equivalence with the antibody, which it does right at the surface of the agar, a precipitation band forms, and as more and more antigen diffuses into the serum-agar the precipitate moves steadily forward with a sharp leading edge and gradually fades out behind

Dr. Wodehouse is an Associate Fellow of the American College of Allergists.
From the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

in the region of antigen excess in which the precipitates are more or less soluble. This is known as the Oudin technique. There are usually more than one precipitation band formed. up to ten, or even more. It is generally believed, as stated by Oudin, that each precipitation band represents at least one antigen-antibody reaction, though, as we shall see, this has been questioned by several investigators. There may be more bands than appear because several may be superimposed or obscured by the trailing zones of those preceding them.

The density of the precipitation band depends only upon the concentration of the antibody; the stronger the antibody the more dense is its precipitate, also the slower the antigen diffuses against it, so that if the antibody is too strong the band may even move upwards into the liquid antigen phase, causing an amorphous precipitate above the meniscus. On the other hand, the concentration of the antigen has little or no effect on the density of the precipitation band but does affect its rate of penetration. The stronger it is the faster it goes.

It has been shown that the diffusion rate is proportional to the square root of the time and to some fractional power of the initial concentration of the diffusing substance. This affords a simple means of comparing the potency of antigenic extracts, which is the primary purpose of the Oudin method.

For qualitative studies the various methods of double diffusion are used. The simplest, also designed by Oudin, is to interpose between the serum-agar mixture and the supernatant antigen extract an intermediate column of plain agar. Though devised by Oudin, this is generally called the Oakley or Oakley-Fulthorpe method,[44] since it was first put to serious use by these investigators. It was first published by Pope et al,[50] giving credit to Oakley and Fulthorpe. With this technique the antigens diffuse downwards and the antibodies upwards, each with its own concentration gradient and, where they meet in the neutral agar between the two sources precipitation bands are formed. These are flat disks usually discrete, serving admirably for qualitative analysis of antigens. One disadvantage of the method is that direct comparison cannot be made between two antigenic extracts or antisera, although this can be done indirectly by comparing them separately and in combination.

The method can also be used quantitatively. Since the position of the precipitation band in the intermediate layer depends upon the relative valencies of its antigen and antibody, if the antigen is partly neutralized by additions of antibody the band will form proportionately higher up. Hence, the potency of antigens may be estimated by their resistance to neutralization by additions of antibody, in moving the band up the column.

For qualitative analysis a more useful method of double diffusion is that of Ouchterlony. It is used in two ways, the punch plate, and the cup plate. For the former, agar is poured into a petri dish so as to make a thin layer. When this has solidified, small templets are placed on the surface and a second layer of agar poured. When this has set, the templets are removed leaving little basins into which the reactants may be poured. In the cup-plate method, penicillin assay cups are substituted for the basins. These are small metal cylinders open at both ends, which are stood on the surface of the agar. In either case the reactants diffuse against each other through the inert agar, each with its own concentration gradient establishing zones of equivalence with their resultant precipitation bands. Any number or arrangement of diffusion centers may be

used according to the comparisons to be made. The most useful, however, appears to be the three-place plate, permitting two antigenic extracts to be compared diffusing against the antiserum of one or the other of them or against a combination of the two antisera. In such an arrangement, if the antigens are identical each will form precipitation bands with the other's antiserum, and these will join with the corresponding bands of the other forming symmetrical arches over the antiserum source. If they are nonidentical they will form bands only with their homologous antiserum, and if diffused against their antisera in combination each forms its own precipitation bands without any interference with those of the other, crossing each other in what is known as the pattern of nonidentity.

Other methods of gel diffusion which have been devised may be found described in the review articles mentioned above. Some offer minor advantages for special purposes, but the Oudin, Oakley and Ouchterlony have been found to best serve all ordinary needs of antigenic analysis and the further development of gel diffusion techniques has been principally extending and developing them.

TECHNIQUES

It had been the custom among investigators using the Ouchterlony system to refill the cups or basins once or twice during the diffusion to enhance the visibility of the precipitation bands. Kaminsky[36] showed that refilling with antigen at a concentration lower than that originally used had no effect, while at an equal concentration it augments the density and causes a slight displacement of the bands with a possibility of their multiplication. Refilling with higher concentrations results in a displacement of the bands and abnormal differentiations. She also showed that it was important to adjust the reactants properly to each other to bring out the complete precipitation pattern. It is not enough to have them adjusted to equivalence because the diffusion coefficients of the antigens also have a marked effect. Consequently, always several different concentrations should be tried.

An approach to the chemical identification of the antigens participating in the precipitation pattern has been made by Björklund.[7,8,9] He showed that antigens when combined with their antibodies retain their affinities for certain dyes, thus affording the possibility of studying not only the chemical nature of certain antigens but also their immunologic behavior in complex mixtures.

After the precipitation patterns on the Ouchterlony plates have fully developed, the unprecipitated reactants are washed out and the plates are treated with selective dyes, such as basic fuchsin, Mayer's mucicarmine and Sudan black.

Ambrose et al[1] report an interferometric method for rendering visible bands which are otherwise too faint to be seen. Optically plane glass sheets are silvered on one side to give about 5 per cent light transmission. These are adjusted with the silvered sides facing each other, almost but not quite parallel. The channel between them is filled with a gel in which the diffusion of antigen and antibody is caused to take place. This is then placed on the microscope stage and observed with parallel monochromatic light from below. Precipitates that are too faint to be seen cause a bending of the interference fringes by virtue of their increasing the index of refraction of the gelatinous medium.

Investigators using the gel diffusion techniques have found great difficulty in recording their patterns. Photographic methods yet devised fail to reproduce all the precipitation bands at one time. Gell[19] uses lantern slide plates as support for the gel medium. After the precipitation pattern is developed the medium is dried down, covered with a plastic coating and mounted as a lantern slide.

Attempts on the part of this reviewer to duplicate this technique leave the conviction that it is not likely to equal even ordinary photography. It appears that the best way yet available for recording these patterns, in spite of the labor involved, is by simple line drawings.[70] They are, of course, not exact reproductions of the patterns. They are, rather, a record of what the observer saw, or thought he saw. It is true that they may be influenced by bias or preconceived notions. In this they do not differ from most other laboratory records, which indeed they are, only in pictorial instead of written form. One important advantage they have over even a perfect photograph, if such were possible, is that a drawing does not have to be based upon a single observation, but may represent a complete record of many observations.

One advantage of the double diffusion technique like Ouchterlony's is that it does not require the use of clear antisera, since its precipitation bands form in inert gel instead of in a serum-gel combination, as in the Oudin technique. Frequently antisera when combined with agar become so opaque that the precipitation bands cannot be measured, but with the Ouchterlony plates quantitative determinations are not possible. Jennings et al[32] have produced a modification which appears to have possibilities in this direction. The plates which they use are in the form of a shallow straight walled dish, of which the sides form an equilateral triangle with vertical notches provided in the middle of each wall. The plate is filled with melted agar. After this has set, the insertion of thin metal blades into the notches serves to divide the agar sheet into four triangular sections, one central and three peripheral, all equilateral and equal in size. The three peripheral areas are cleared of agar, the blades removed and the cleared areas refilled with agar combined with antiserum in one and with the antigens to be compared in the other two.

Besides the advantage of having the precipitates form in plain agar other advantages accrue from the long straight contact faces between the reactant sources and the arena of their inter-reaction. These lead to the development of rectilinear zones of precipitate emerging from the two basal angles of the central triangle. The point at which these two lines intercept results from the relative concentrations of the two antigens; consequently, it can be used as a measure of their relative activity. As the authors point out, this point can be determined far in advance, as soon as the directions of the lines have been established, which may be after as little as two hours. Thus, they say, "The advantages peculiar to the Oudin method will be added to those of the double diffusion techniques."

Attempts on the part of this reviewer to repeat these experiments leave the impression that an inherent weakness of this scheme lies in the incompatibility of a non-rigid substance like agar gel with the geometrical accuracy required of its shaping. However, the scheme is reminiscent of Elek's two filter paper strips, one impregnated with antitoxin imbedded in the agar, the other impregnated with toxin on the surface of the agar crossing the lower strip at right angles. As with

Jennings', Elek's precipitation bands form in rectilinear streaks emerging from the angles that one filter paper strip makes with the other. Elek points out that the angle of incidence of the precipitation streak to the edge of the antitoxin strip is determined by the relative valencies of the two reactants. Consequently, a third strip of filter paper also vertical to the serum strip and bearing another antigen should be expected to permit comparison of two antigens in essentially the way Jennings describes.

Refinements and modifications of the Oudin technique have appeared. Ordinarily the tubes are kept at constant temperature in an air-conditioned room, an incubator or refrigerator depending upon the nature of the materials used. They are read at room temperature with oblique illumination against a black background and the distances of penetration of the precipitation band measured by a vernier caliper, reading to 0.1 mm, held against the outside of the tube. The error by this method is about ± 0.2 mm. Jennings[30] reports keeping the tubes in a constant temperature water bath with optically plane glass walls at a temperature of 45° C. The tubes are read, without removing from the water bath, by means of a Cathetometer which reads directly to 10μ and a third decimal place may be estimated. Illumination is from behind and below a special holder bearing the tubes. Such precision instruments, it would seem, must greatly exceed in refinement the method itself.

Surgalla et al[57] have devised an antigen comparator constructed of plexiglass for testing four different antigen mixtures over a common reservoir of serum-agar. The latter is placed in the lower part of the cell with the four menisci extending slightly above the lower ends of the three partitions in the upper part. The antigen mixtures to be compared are placed in the four upper compartments. An advantage of this arrangement is that in case two or more bands, originating from one antigen, are superimposed, as often happens with the Oudin technique, these may be resolved by varying the concentration of the antigen mixture. The use of this little gadget apparently extends the Oudin technique into the qualitative field, in which it can hardly hope to compete with the techniques of Ouchterlony and Oakley.

Muñoz and Becker[43] have shown that chickens can serve for the production of antisera as well as horses and rabbits, which have been most generally used. The authors chose chicken serum because they were studying the precipitation systems of edestin which is a vegetable globulin requiring for its solution 8 per cent NaCl, with which chicken serum is compatible but others are not.

Possibly the most important innovation in the techniques of gel diffusion is that of Grabar and Williams[25,26] combining electrophoresis with gel diffusion. A gelatin or agar gel is prepared on a carefully levelled glass plate, with pieces of filter paper imbedded at the ends to complete the junction of the gel sheet with the vessels which contain the platinum electrodes. The material to be analyzed is combined with gelatin at 40° C and poured into a basin moulded or cut into the gelatinous sheet. Electrophoresis is done in a closed container at ordinary temperature for fifteen to eighteen hours. When stopped, one cuts in the gelatinous plates, parrallel to the direction of migration a narrow groove, which is then filled with the homologous antiserum. This, upon diffusing into the gel forms precipitation lines as in the Ouchterlony technique. Each component of a mixture of antigens gives an independent

precipitation band which can be distinguished by its immunologic specificity and defined by its relative electrophoretic mobility.

Scarcely two years after Grabar and Williams brought out their immunoelectrophoretic analysis in gelatinous medium, Scheidegger[55] devised what appears to be a most useful modification of it for microanalysis. For the original large glass plate Scheidegger substitutes a microscope object slide, 76 by 26 mm. On this is poured exactly 2 ml of the gelatinous medium. When this has set, two round holes are punched in it by means of two 10 gauge injection needles with their bevels cut off and held appropriately spaced in a cork. The holes are made at the center of the slide astride its longitudinal axis, and along the latter is cut a strip 1 mm wide and 3 mm long. The gelatinous medium is sucked out of the two holes but allowed to remain in the central strip. The holes are then filled with the antigens to be tested, and subjected to electrophoresis at about 6 V/cm for forty-five minutes, after which the median strip is sucked out and the groove thus formed is filled with 0.005 ml of the immune serum. After about one half hour the first lines become visible. After twelve hours the pattern may be considered complete.

The preparations may be photographed by direct contact on paper or film or by utilizing the slide as a negative in a photo-enlarging apparatus. Or the slides may be dried and stored indefinitely, and at any time restored by simply wetting them. The pattern can be enhanced by staining with appropriate dyes such as amido black 10B or azocarmine.

The amount of antiserum involved in this method is so small that blood may be obtained from the smallest laboratory animals or from a prick in a human finger.

NUMBER OF PRECIPITATION BANDS PER REACTION

Both Oudin and Ouchterlony have repeatedly asserted that each precipitation band represents at least one antigen-antibody reaction—more sometimes because bands may be superimposed, presenting the appearance of a single one. This concept is fundamental to the underlying theory of gel diffusion. The formation of precipitate in the region of equivalence, by the very nature of the reaction, constitutes an impenetrable barrier to either reactant which produced it. The precipitate itself is not the barrier. Indeed it offers no hindrance to the passage of other antigens and antibodies. It merely marks the position of the region of equivalence which is the real barrier since it is the region where the two reactants unite and are removed from the field of action. Without these conceptions the phenomena of gel diffusion would be meaningless. Yet Jennings[31,32] suggests that antigen, after reacting with one antibody for which it bore a specific determinant group, might still diffuse to form concentration gradients beyond the line of visible precipitate from the first reaction. Thus, equivalence with a second, more dilute antibody by virtue of a second specific determinant group, might lead to the formation of a second Oudin zone.

Wilson and Pringle[66] present an alternate hypothesis stating that it is conceivable that multiple zone patterns may represent a manifestation of rhythmic diffusion phenomena, which was the original interpretation of Bechhold in 1905, since disproved by Oudin, Ouchterlony and others.

The multiplicity of antigens revealed by the double diffusion technique has certainly come as a suprise to all who have weighed the evidence, and

their significance is not yet fully understood. We would do well to heed Wilson and Pringle's admonition that "they should impose great caution in the evaluation of results obtained with this technique." On this subject Ouchterlony[46] says, "An antiserum obtained by immunization with a single antigen can give rise to a precipitation spectrum containing more than one line." and elsewhere ". . . it is concluded that the precipitation patterns observed indicate the presence in the serum . . . of a variety of antibodies of different degrees of specificity some reacting with one or more of the related or modified antigens, some with the homologous antigen only." The present reviewer[70] has discussed this phenomenon in connection with the specificity of the ragweeds and shown there that it is consonant with the specificity of serologic reactions as set forth by Landsteiner. The outstanding feature of the gel diffusion technique is that through its amazing specificity it can reveal antigenic and antibody differences that were only simply foreshadowed by other such techniques as chromatography and electrophoresis.

PHYLOGENY AND SPECIFICITY

It has been shown by Kendrew et al[38] that myoglobins after being repeatedly crystallized can be used as antigens and studied with gel diffusion techniques. They prepared antiserum in rabbits against myoglobins of sperm whale *(Physter catodon)*. When the γ-globulin solution prepared from pooled antisera was used in Ouchterlony plates diffusing against the myoglobins of sperm whale and fin-back whale, three distinct bands were formed in the pattern of partial identity. These results suggest that myoglobin prepared by rigorous methods of purification consists of more than one component. This anti-sperm whale serum crossed freely with myoglobin of other members of the Cetacea, but only slightly with those of seals *(Pinnipedia)*, and not at all with those of other orders, whereas the antisera against seal *(Phoca vitulina)* myoglobin cross reacted with that of other members of the Pinnipedia but not with that of other orders. "The range of purified myoglobins from various animal species is wide, and this protein would probably lend itself well to detailed investigation of species specificity."

ORGAN SPECIFICITY

Björklund[5] makes use of a modification of the Ouchterlony technique in an extensive study of the antigens of bone marrow as compared with those of the lung and spleen. He says, "It may be claimed on principle that identical antigens are capable of suppressing each others' precipitation lines. The method can therefore be used for checking and supplementing Ouchterlony's identity reaction." His modification is inhibition by pretreatment of the diffusion medium with the plasma antigens common to all, thus simplifying the precipitation patterns. By this technique he showed that certain antigens were common to these organs, others not.

In this paper the author lays down a set of rules for standardizing the double diffusion technique, such as the prevention of evaporation, uniform composition of the gel, constancy of temperature et cetera. He says, "With a technique standardized in these respects gel precipitation yields results easy to interpret and easy to reproduce." "It should also be remembered that antigen present in the insoluble state or otherwise resisting diffusion will altogether defy observation. . . . The last mentioned circumstance is actually the most important and, as far as is

known, the only disadvantage of gel diffusion. In most other respects (sensitivity, selectivity, resolving power) gel diffusion is far superior to the older methods."

Roa et al[52] using double diffusion by the Oakley technique found that bovine lens vitreous and aqueous proteins were different from serum proteins, and they suggest that, since lens proteins are antigenically different from blood proteins, this may explain the possibility of sensitization to one's own lens protein resulting in endophthalmitis phacoanaphylactica.

Wieme and Kaminski[63] studied the proteins of bovine crystalline by the immuno-electrophoretic method of Grabar and Williams. They demonstrated the presence of at least eight different antigens. These they were able to relate to the fractions previously found by paper electrophoresis.

PURIFICATION

Pope et al[50] in their work on the purification of diphtheria toxin and antitoxin used the double diffusion method in tubes which they credit to Oakley (unpublished). They found by their precipitation bands that culture filtrates from *C. diphtheriae* contain at least twenty-four antigens, and that routine peptic-refined antitoxin contain corresponding antibodies. A preparation received from Pappenheimer gave fourteen precipitation bands. However, they were able to reduce the number of bands in their purified preparation to only three, one of which represented the toxin itself.

They say, "In our opinion this method has proved to be invaluable as a means of elucidating the antigenic structure of diphtheria toxin filtrates and as a guide to the purification of both toxin and antitoxin."

Relyveld et al[53] used the same technique as Pope to follow the purification of their diphtheria toxin. They demonstrated that, as already shown by Pappenheimer, Lepow and Pillemer, the characteristics of the final product depend upon the medium used for the preparation of the toxin. By suitable methods of purification they were able to reduce the number of precipitation bands from eight to four, representing at least as many antigens.

Grabar et al[24] used the double diffusion in the Ouchterlony plates in their study of the antigenic constitution of normal leukocytes and leukemic leukocytes. The method was used more or less successfully in freeing the leukocytes of all other blood elements. They used five-place plates with anti-whole blood serum in the central cup and purified fractions around it, taken at successive stages in the purification process.

Ormsbee et al[45] used a similar technique in the purification of *Bacterium tularense* antigens. "The result indicated that at least three, and possibly five, antigenic constituents originally present in the initial supernatant had been eliminated during the purification process."

Surgalla et al[57] used their "antigen comparator" to follow the progress of fractionation of Staphylococcal entero-toxin.

Ransom et al[51] used a two-celled comparator, modified from Surgalla's, in studying the strains of *Pasteurella pestis*. With this device they ascertained that the merging of precipitation zones is a criterion of homogeneity; crossing zones of heterogeneity. By these criteria three groups among five strains of *P. pestis* were established.

BACTERIA AND TOXINS

Tunevall[60] studied the antigenic structure of *Haemophilus influenza* using Ouchterlony plates. It was found that various strains possess antigenic components common to or widely distributed within the species. Such components were found both in extracts of the bacilli and released from growing cultures. But the extracts contained only traces of some components of the cultures which were presumably derived from the capsular substance. Type specific strains derived from rough strains did not show any antigenic differences except that the former possessed a component identified with capsular substance.

Björklund et al,[10] studying *Clostridium* toxins, found that each gave a typical precipitation pattern, with one major band and one to eight minor bands. Reciprocal and non-reciprocal reactions were observed between different types and species, producing antigenic components which are to be regarded as group, species and type specific.

Guillaumie et al[28] in their studies of *Clostridium* prepared toxins from *C. histolyticum, C. septicum* and *C. oedematiens* and their antisera in horses. Using the Oudin technique they demonstrated seven precipitation zones in each. Most of the sera collected in the first few months were specific, but if the injection of *C. histolyticum* is long continued often one obtains complex antihistolyticum serum having the property of neutralizing *septicum* toxins.

Chen et al,[14] in their studies on immunization against plague, used a modified form of the Elek technique, that is to say strips of filter paper impregnated with antiserum imbedded in agar. For antiserum they used anti-pasteurella gamma globulin. The bacterial antigens were diffused from living cultures streaked on the surface of the agar across the filter paper strips.

By testing combinations of *P. pestis* and *P. pseudotuberculosis* against anti-P. pestis gamma globulin two precipitation reactions common to both were demonstrated. They also showed that the rough somatic antigen reported to be common to both organisms is in fact two somatic antigens, and that only two major antigens are specific for *P. pestis.* The result substantiates the idea that virulent strains do not possess a special virulence factor, but that the virulence is related to the amount of a certain factor in the organism.

DISEASE STATES

Gel diffusion techniques have been used in the study of disease states both experimentally and clinically, in such diseases as cancer, rheumatic diseases, diphtheria and allergy.

Björklund[6] prepared an antigenic extract from dried human cancer which he used to produce a precipitating serum. When this was diffused against the antigen numerous precipitation bands were formed. By pretreatment of the medium with normal human serum, the precipitation bands due to normal human serum constituents could be suppressed, leaving only those due to the cancerous tissue.

Darcy[16] found it possible to distinguish the plasma of rats bearing transplanted or induced tumors from that of normal rats. When cancer plasma and normal plasma were compared diffusing against antitumor serum, made from the plasma of animals bearing the Walker tumor, several weakly developed groups of bands and one very marked band were present on the cancer side of the precipitation arch but

absent on the normal side. Normal bands could be suppressed by Björklund's inhibition technique. The ability of the plasma to produce these manifested itself as early as six days after implantation of the Walker tumor. Besides these extra precipitation bands there was also found considerable disturbance in the pattern of the other bands, indicating that some antigens were appreciably increased and others diminished in the cancer plasma.

Korngold et al[39] examined a human carcinoma which had been grown for many generations in rats, eggs and hamsters. The Ouchterlony technique showed that the same human antigens were always present regardless of the number of generations that the tumor had been grown on the foreign hosts. The same authors,[40] in their studies of breast carcinoma, showed, by means of Björklund's staining technique, that the precipitation bands obtained with lipoprotein could be identified by staining with Sudan Black B or Oil Red O.

Slater et al[56] carried out a study of 21 myeloma sera to determine the relationship of their components to those of normal γ-globulin and to each other. Ten proteins were separated for detailed characterization. Every one of the myeloma proteins was different and individually specific. It appeared that the γ-myeloma proteins were all related to normal γ-globulin or one of its fractions and, although different in each patient, were related to one another. The β-myeloma proteins were likewise interrelated despite physical differences, and formed a distinct group. They used the Ouchterlony technique and a modification of that of Grabar and Williams using starch as the supporting medium.

Grabar et al[26] used their immuno-electrophoretic method for the study of myelomas. They found that they could be classed as β and γ myelomas according to which of the serum globulins was affected by them.

Burtin et al[12] reported that for detecting Bence-Jones proteins the double diffusion method of Ouchterlony greatly surpasses both the classical thermic detection and paper electrophoresis in sensitivity and specificity. They also established by the same techniques that the Bence-Jones proteins are not identical among themselves and can be classed into three groups.

Fischer[17] points out that during the past decade increasing attention has been paid to the possible relationship between variations in the concentration of gamma globulin in the blood serum and disease states. He reports a case of agammaglobulinemia. This patient, a four-year-old boy, was unusually susceptible to septicemia and infectious diseases. He was given 2 gm of gamma globulin every four to six weeks, and since then has shown normal or possibly even better than normal resistance in infections. The author says, "If a microchemical method for the determination of plasma proteins can be adapted to the quantitative determination of gamma globulin, it should be particularly useful in studying this problem." It appears to this reviewer that the Oudin technique offers such a method.

Halbert et al[29] in their study of human streptococcal infections, found that rabbit antisera after the first course of immunization with Streptolysin O frequently showed only one precipitation band by the Oudin technique, while those obtained after the total series of injections showed up to four bands. Of 143 human sera tested with the same streptolysin concentrate, ninety-four showed precipitation bands. Of these sixty-eight showed one, twenty-three showed two and three showed three such bands.

The authors conclude that the data strongly indicate that streptolysin O activity in human sera is generally due to precipitating antibody and that nonspecific inhibitors are usually not involved.

These authors also showed by double diffusion technique (Ouchterlony and Oakley) that human serum may contain from 0 to 5 antibodies against antigens present in their streptolysin-O preparation, and from 0 to 7 antibodies against the antigens in a concentrate of the streptococcal culture supernate.

Rheumatic subjects showed antibody responses to many more antigens present in these preparations than did nonrheumatic subjects.

Evidence was obtained which indicated immunologic specificities of streptococcal desoxyribonuclease from Group A and from Group C streptococcus.

Kuhns,[41] investigating immunization by diphtheria toxoid, showed that subjects so immunized developed a marked skin reactivity to toxoid with or without associated nonprecipitating antitoxin. Eight skin-sensitizing sera were tested but none formed precipitation bands, showing that the skin sensitizing antibody is probably not the same nor even related to the precipitating antibody.

Frandsen et al[18] seeking precipitating antibodies in allergic human sera found that 1 per cent extracts of such allergens as horse dander, feathers and danders, grass pollen and hormodendrum failed to precipitate with sera from sensitive cases. Only if the concentrations were increased up to 5 and 10 per cent were precipitates obtained, but then these also gave precipitates with the nine out of ten normal sera, showing that the method could not be used for the diagnosis of allergy.

Augustin[2] appears to have had somewhat different experience. Thus she says that diffusion rings have been obtained with human sera from grass-pollen sensitive subjects.

VIRUSES

Only two reports of the use of gel diffusion technique in the study of viruses were found.

Jensen and Francis[33] obtained antisera from ferrets convalescent from influenza and from rabbits immunized by intramuscular injections of allantoic fluid of eggs infected with one of the strains of influenza virus. With these they were able to produce precipitin bands with both the Oudin and Ouchterlony techniques, which were strain specific. It required three weeks' incubation for the bands to develop and they formed very close to the virus source. They say that care must be taken to prevent the reaction from occurring in the cups rather than the agar.

Gispen[20] used pox virus in a similar way. Choriallantoic membranes of duck embryos were infected with pox strains. Three days later these were extracted in saline and the extract used in inoculating rabbits. Using the Oakley technique he showed that the diffusion pattern of vaccinia antigen against standard vaccinia serum produces three to six zones of specific precipitate.

VENOMS

Piantanida et al,[49] studying the antigenic structure of the venom of the sand viper, *Viper ammodytes*, of southeastern Europe, found that the Oudin test gives evidence of the presence of three antigenic com-

ponents. The same tests with fractions precipitated at three different salt concentrations showed that all are partially precipitable at low ionic strength.

EMBRYOGENETIC AND DEVELOPMENTAL CHANGES

Gel diffusion provides a simple method of studying the changes that take place in animals during their development from the egg to maturity. Cooper,[15] studying the development of frogs by the Oudin technique, found at least five to seven antigens in the egg and neural plate of *Rana pipiens* which are represented by substances with immunologically related combining groups, but not identical with them. The latter contains one or two more antigens.

Ten Cate et al[59] in studies of the development of the eye lens in chicken and frog embryos, found the presence of adult lens antigens in the chick embryo at sixty hours and in the frog at nineteen to twenty hours. They conclude that chemical differentiation precedes morphalogic.

Telfer and Williams[58] studied the changes in the blood antigens of the Cecropia silk worm, (*Platysamia Cecropia*) using a modified Oudin technique. The maximum number of bands developing was nine, one of which was identified as a carotenoid protein. In order to simplify the problem of identification of the bands three antisera giving fewer bands were selected for detailed study. Between them these three antisera reacted with six different pupal blood antigens to form six conspicuous and readily distinguishable bands. Five of the six corresponding antigens were found to be present throughout metamorphosis. The sixth appears in the blood late in the fifth instar, persists during the pupal stage and disappears in the adult. "The six antigens undergo a general increase in concentration during the last larval instar and a decrease in concentration during adult development . . . each antigen undergoing a distinctive pattern change." "These results indicate that the quantitative changes in the blood antigens result from physiological processes which produce changes in the concentration of individual blood antigens without necessarily affecting the concentrations of the other antigens . . . and that the growing tissues of the silk worm can selectively accumulate or utilize individual antigens."

This work would well serve as a model for future studies of antigens in development.

Kaminski et al[37] studied the constituents of eggs during incubation using the technique of Grabar and Williams. They found that the proteins of egg white, ovalbumin, ovomucoid, ovoglobulin and conalbumin constitute the major portion of the total proteins and persist together with the serum constituents right up to hatching.

FOODS AND ALLERGENS

Kaminski,[35] using the Ouchterlony and Grabar-Williams techniques, was able to identify the precipitation bands corresponding to the principal constituents known to be present in egg white, also to establish the presence of antigenic constituents not previously known. Those of various species of birds were also compared. It was found that conalbumins and ovalbumins were the least specific; among others the identity between the ovalbumins of chicken and emeu was established. On the other hand one of the globulins seemed to be different in each species.

Vaughan and Kabat[61] in their studies on the skin-sensitizing antibodies in rabbit antisera used the Oudin technique to provide a minimal estimate of antibodies in a given serum. They showed that the passive transfer of skin sensitization by rabbit anti-egg-albumin serum is independent of antibodies against egg-albumin. They were able to suppress either system without altering the other. Evidence was presented to show that the skin-sensitizing antibodies resulted from trace impurities present even in the highly purified crystalline egg albumin used for immunization. They express the hypothesis that there are in egg white a limited number of antigens, possibly only two, that are capable of eliciting skin-sensitizing antibody. These antigens appear to contaminate crystalline preparations of both egg albumin and conalbumin and are mior components of egg white. Antibodies against the four major constituents—egg albumin, conalbumin, ovomucoid and lysozyme—appear to have skin-sensitizing capacity in human beings.

They estimate the specific antigen which stimulates the skin-sensitizing antibody at less than 1 per cent of the total protein of egg white.

The antigenic structure of the commoner allergenic extracts have been examined by Wodehouse.[67-72] Both the Oudin and Ouchterlony techniques were used. Interpreting each precipitation band as representing one antigen-antibody reaction, a similarity of structure was found in all. Each possessed a major antigen, not necessarily homogeneous, and about six or eight minor antigens (occasionally more or less). The antigens of tall and short ragweeds (*Ambrosia trifida* and *A. elatior*) were found to be not identical but closely similar.[70]

The more prominent of the precipitation bands were identified with fractions prepared by other investigators by chemical fractionation, electrophoresis and chromatography.[71]

The major antigens of the six common hay fever grasses, except one, were found to be practically identical.[70] All had some minor antigens identical and some nonidentical. Bermuda grass was exceptional. With this the major antigen was found to be nonidentical, and only one or two of its minor antigens even slightly similar to those of timothy. But each possessed what is believed to be a heterophil antigen to the other.

Several house dust extracts obtained from both similar and different sources were found to have identical or nearly identical major antigens but more or less nonidentical minor antigens.[69]

Trichinella extract was found to give ten well-marked precipitation bands.[72] In the double diffusion plates these formed in two closely associated groups and one detached band, suggesting the presence of two distinct groups of closely intrarelated antigens, and a single dissociated antigen. The effect upon these of the various physical and chemical agencies used in the preparation of diagnostic extracts was examined, also interreactions with allied forms and various pathogenic bacteria.

BLOOD ELEMENTS

Gel diffusion methods have been used by several investigators in studying the protein of human and animal bloods. Kabat et al[34] used the Oudin technique in their study of human gamma globulin. Rabbit anti-γ-globulin serum was absorbed by adding crystalline human serum albumin until no further precipitate occurred. The absorbed anti-sera were then tested by the Oudin technique, combining the antiserum with

the gel and overlaying it with undiluted human serum. As diffusion proceeded into the agar, only one band of precipitation could be observed. This corresponded to a band produced by laying γ-globulin over the same serum-agar mixture. This, the authors say, indicates that the absorbed antiserum contained antibody only to the γ-globulin.

Burtin[11] put the technique of Ouchterlony to the test for the study of human serum albumin. It was found to be necessary to have both reactants in the precipitating system adjusted as closely as possible to concentrations of equivalence or take account only of the initial aspects of the precipitation patterns. He states that the secondary division of the precipitation line given by the serum albumin does not necessarily indicate the complexity of this antigen. It is probably due to an immunologic artefact.

Burtin et al,[13] making use of the Ouchterlony technique, together with that of Grabar and Williams, examined the γ-globulin of human serum. They say that, thanks to these techniques, they were able to attribute to haptoglobine an immunochemical personality, and that it has an independent existence in human serum.

Gitlin,[21] studying human β-lipoprotein by means of the Oudin technique, found that when various concentrations of the β-lipoprotein were layered over its homologous antiserum five or six bands were readily revealed indicating heterogeneity of their lipoprotein.

Grant et al [27] in their study of the role of lipoprotein in atherosclerosis established identity between the lipoproteins of normal human sera and those of atherosclerotic rabbits and human patients, thus showing that, although lipoproteins are quantitatively increased in the sera of atherosclerotic patients, the gel diffusion plates prove them to be qualitatively identical.

They used the Ouchterlony technique and their figure shows each lipoprotein producing a single sharply defined precipitation band joining with the other to form a nearly symmetrical arch. The antisera used were obtained from the blood of chickens immunized with lipoprotein of rabbit and human origin.

Korngold et al,[40] in their studies of human β-lipoprotein by double diffusion technique, showed that the precipitation bands containing lipoprotein could be specifically stained by Sudan Black B or Oil Red O, making it possible to single out the precipitation lines due to this protein which Gitlin was not able to do by the Oudin technique. Hence, they say, "no evidence was presented that all the antigens responsible for these lines were lipoprotein, and consequently his results may have been due to contaminating proteins."

STANDARDIZATION

Rubenstein[54] studied egg and serum albumins by the Oudin quantitative technique. He confirmed the linear relation between the logarithms of the antigen and antibody concentration and their penetration rates, and proposed a empirical equation for egg albumin and bovine serum albumin systems.

The present reviewer showed that the quantitative technique of Oudin could be applied to the standardization of pollen extracts,[67,68] house dust[69] and trichinella extracts,[72] in spite of the fact that there are always several to many antigens involved. Only one of these can be used at a time for standardization, but the values obtained can be taken to cover the

others providing the extract has its normal complement of antigen. This can easily be determined by comparing its precipitation pattern with that of the standard extract by double diffusion plates.

A modification of the quantitative application of the Oakley technique has been presented by Augustin et al.[3] Serum-agar of constant concentration is placed in a series of tubes. Over this is layered a column of plain agar exactly 0.5 mm long. The tubes are then incubated at 37° C for fifteen hours to allow the antibody to enter the neutral phase in advance of the antigen. A series of antigen dilutions are then poured on, and the precipitation bands form in the neutral phase. The weaker the antigen the higher up the band is formed, so the dilution which causes the band to appear just on the upper boundary of the neutral column may be considered the end point.

The present reviewer, in attempting to repeat Augustin's technique, found it too difficult for practical purposes to adjust the intermediate agar column to a uniform length, which obviously must be very exact. However, it was also found that if the length of this was measured for each antigen dilution, and its deviation from the mean of 0.5 mm calculated, it could be applied as a correction factor to the distance of the precipitation bands from the upper boundary of the middle column. Tolerably straight curves were obtained when these corrected values were plotted against the logarithm of the antigen dilutions.

This brief survey of the literature of gel diffusion shows beyond question that during its short history of less than ten years, it has become firmly established in nearly all branches of immunology. It is the vigorous offspring of two old, reliable and thoroughly respectable parents, precipitin and diffusion. This survey shows that it inherits these attributes from its forbears. It is now in the hands of a group of, for the most part, brilliant young scientists, and may be expected to immeasurably increase our understanding of immunologic processes.

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FELLOWSHIP IN ALLERGY AVAILABLE

An opening is available for a Fellowship in Allergy at Northwestern University Medical School. This provides a combination of clinical and investigative work in allergy for training in specialization, and is approved for credit by the Board of Internal Medicine and the Sub-specialty Board of Allergy. Annual stipend is $3,000. A Residency in Allergy is also available at the Veterans' Research Hospital, providing for service equally divided at the hospital and the medical school. For details and application blank, write to Dr. S. M. Feinberg, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11, Illinois.

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Letter to the Editor

To the Editor,
Annals of Allergy:

As a doctor, as an allergist, and as a member of The American College of Allergists of which the ANNALS OF ALLERGY is the official journal, I feel duty-bound to comment on the article by M. Coleman Harris appearing in the November-December, 1955, issue of that journal entitled, "Is There a Specific Emotional Pattern in Allergic Disease?" Dr. Harris' answer to his own question is that there is not. How he arrives at this answer provides the basis for the need to comment.

On pages 654 and 655, Dr. Harris cites as evidence against a "pattern," numerous authorities who have written on the emotional factors in allergic disease. He enumerates the particular emotional "causes" which these authorities have discussed. For example—Wilson, repressed olfactory sexual impulses; Saul, intensification and frustration of passive receptive wishes; French and Alexander, insecurity; Fromm-Reichman, repressed hostility and frustration in intellectual rivalry; Alvarez, painful emotions, conflict, anger, and frustration in love; Macalpine, suppressed anger; Miller and Baruch, maternal rejection; et cetera. He speaks as if each authority considered these as disparate emotions. As if each, in and by itself, is the ultimate cause. In other words, he does not differentiate between the varying factors in an underlying pattern or syndrome and the *immediate* trigger or cause. It is as though he would quote authority A as claiming that foods are the cause of asthma, authority B that pollens are the cause of asthma, and authority C that infections are the cause of asthma, and concludes thereby that there is no underlying pattern, viz. the allergic constitution. Perhaps more confusing still, the statements of the various authorities are put forward by Dr. Harris in a way that suggests that each authority dismisses the ideas of every other authority so that each authority becomes a protagonist of Dr. Harris in opposing the possibility that an underlying pattern exists.

Dr. Harris is particularly concerned with the factor of maternal rejection as a "cause" of bronchial asthma. He has gone to considerable effort to disprove its importance as an etiologic emotional factor in allergic disease and apparently feels that such disproof is essential to his argument that there is no specific emotional pattern in allergic disease. His thesis is best stated in his own words, "Theorizing still further, it would seem that if maternal rejection were an important cause of bronchial asthma in children, the juvenile homes of the country, where children who certainly have been rejected are placed, would be flooded with asthmatics. This is certainly not the case in San Francisco. Last year (1954), 6,986 children came under the jurisdiction of the San Francisco Youth Guidance Center (Juvenile Hall) and were examined in the medical department. These children ranged in age from two months to eighteen years of age. Of the 6,986 seen, but five cases of bronchial asthma were diagnosed: two boys and three girls. This roughly is .06 of 1 per cent. So far this year (January 1, to March 28, 1955), 1,184 children have been reported ill, and only two with bronchial asthma!"

From this statement, it is obvious that Dr. Harris' argument is as follows: Here is a large group of children exposed to maternal rejection. Maternal rejection is said to be an important factor in bronchial asthma. But in this group there is little asthma. Therefore, maternal rejection has but little to do with bronchial asthma and those who claim otherwise are mistaken. Obviously, the only

thing that this argument proves is that maternal rejection can be present without causing asthma but it does not prove that asthma can be present without maternal rejection.

As a matter of fact, it would be surprising if the number of symptomatic asthmatics in the population studies by Dr. Harris showed as much as a normal incidence of asthma. And, as a matter of fact, it does not. It shows a surprisingly low incidence, lower than normal. If the same kind of reasoning were followed, Dr. Harris might argue that maternal rejection prevents the appearance of asthma.

To the well-informed person, the low incidence of asthma in a juvenile hall population might be anticipated. The majority of children are sent to a juvenile hall for delinquency, which is an acting out in anti-social behavior of emotional problems. The allergic child seldom acts out his emotional problems. He is generally a passive-dependent, non-aggressive child who gives expression to his emotional difficulties through bodily illness. Therefore, he is unlikely to appear in a population of delinquents. By the same token, a child who does act out his emotional problems in delinquency does not need to turn his hostility on himself, but is patently capable of taking it out on society and so he does not become ill. Even the occasional asthmatic delinquent may be free of symptoms during a period of acting out as, for instance, the notorious Chessman who had asthma only while living at home and on his good behavior.

Certain questions as to methodology in the author's investigation also come to mind in judging the validity of the statistics which he presents. Not all children in a juvenile home are delinquents. A certain per cent are non-delinquents remanded to the home for custodial care only. This must certainly be so in San Francisco, for the author states that the age-range for the population is from two years to eighteen years. It would be interesting to know whether or not the five cases of asthma reported were custodial cases or delinquency cases.

For a proper presentation, it would also seem that the author should have given in a bit more detail how the presence of asthma or, for that matter, other allergic symptoms were ruled out by medical examination. Whether extensive medical histories were obtained and whether satisfactory histories were obtained from the parents when the children were too young or negativistic.

From these comments on conceptualization and methodology, considerable doubt is thrown on the validity of the evidence and the proof that maternal rejection is not an important source for emotional factors related to allergic manifestations. Nor has any proof been brought forward (whether maternal rejection is present or not) that there is no specific emotional pattern in allergic disease. On the other hand, Miller and Baruch and many others, in their extensive reports on research into the emotional factors in allergy, have shown that such a pattern does exist, that it is an integral but not a separate part of the allergic syndrome, and that it is operative generally only in individuals who are constitutionally predisposed to allergy.

Throughout Dr. Harris' paper, there is apparent an attitude of derisive scepticism which at times causes him to transcend the boundaries of objectivity. I quote the following paragraph:

"Psychotherapy is a valuable adjunct in allergic therapy, but it should not be used as a curative measure to the neglect of the actual etiologic factor which is organic. It would be cruel to deny the patient the relief he might obtain from an allergic investigation, immunization and medication, by focusing his attention on the emotional factors in his illness. There is no specific emotional pattern in allergic disease that has been convincingly proved."

The general implication of this paragraph is that those who believe that the emotions play a part in allergic disease *pari passu* must neglect organic treatment.

There is grave doubt that any of the authorities quoted, such as French and Alexander, Miller and Baruch, Saul, Fromm-Reichmann, Alvarez, and others, will accept this accusation. Their writings attest to the contrary. Not one would subscribe to the implication that emotional factors rule out organic ones or, for that matter, that organic factors rule out emotional ones. Not one would subscribe to organic factors' being neglected. However, they would subscribe to a paraphrase of the author's words as follows, "It would be cruel to deny the patient the relief he might obtain from taking the patient's emotions into consideration."

The final sentence of the paragraph is a non-sequitur which finds no substantiation in the body of the article. It is, if anything, a summation of a very evident unwillingness to conceive of the allergic syndrome as having as well-defined emotional characteristics as it has organic ones.

In summary, Dr. Harris' article may be described as a polemic, an impassioned argument against something or somebody. Emotion has played too important a role, in planning the work, in carrying it out, in drawing conclusions from it and most unfortunately in its manner of presentation.

One questions the good taste of offering such phrases as: "Psychosomatic medicine in this instance (the emotional component of allergy) appears to be on the filmy fringe of allergy." "Studying psychologists' reports, one is struck with the number of times such statements by patients are eagerly grasped by psychologists as bona fide proof that the train of events happened just that way. It would even seem that some psychologists *encourage such allegations.*" (The italics are by the present writer.) Actually, anyone familiar with the methodology of psychotherapy knows with what particular care such intimated *post hoc* reasoning is avoided. How meticulously the therapist gathers his evidence. Not generally with the help of the patient but generally against great resistance on the part of the patient. How he, like "the research scientist checks and rechecks again and again to be sure of his findings." One wonders whether such gratuitous insults to a profession closely allied to medicine belong here. Moreover, since most of the authorities quoted as favoring the presence of emotional factors in allergy are doctors of medicine, one wonders about medical ethics. A judgmental statement such as, "I am persuaded that seldom are they not serenely content and rarely do they delve further for corroboration or contradiction," may perhaps be explained on the basis of the intensity of the belief it intends to express, but it would seem that such intensity of emotion should find expression elsewhere. Nor are statistical data more certainly validated by placing an exclamation point after such statements as ". . . and only two with bronchial asthma!"

Perhaps the most disconcerting aspect of Dr. Harris' paper lies in his apparent acceptance of the concept that the emotions can cause a disturbed physiology, while at the same time continuously disapproving those very authorities who have helped to create and confirm this concept. This disturbing technique lends itself well toward destructive ends but not to constructive ones.

The comments which have been made on Dr. Harris' paper are merely highlights intended to show his general approach and attitude toward the subject which he set out to discuss. It would be deplorable that such evident lack of sophistication concerning modern psychodynamics should, through an emotional appeal, induce allergists and others to close their minds to the fact that a human being is more than a mechanical device which sometimes gets out of order.

Sincerely yours,

HYMAN MILLER, M.D.

Beverly Hills, California
January 9, 1956

News Items

SECOND CONGRESS OF THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

The second congress of the International Association of Allergology was held at the Hotel Quitandinha in Petropolis, Brazil, forty miles east of Rio de Janeiro, in a beautiful mountain setting, November 6 to 13, 1955. The summer home of Don Pedro II and Empress D. Teresa Cristina during their stay in Petropolis, the Hotel Quitandinha is one of the most magnificent engineering feats performed in Brazil.

Guests of honor at the congress were Sir Henry H. Dale of London, England (whose paper was read in absentia); Dr. Robert A. Cooke, New York, New York; Dr. Carlos Jimenez Diaz, Madrid, Spain; and Dr. Mauricio Rocha e Silva, Sao Paulo, Brazil.

The organizing committee of the Brazilian Allergy Society, in charge of arrangements for the congress, was composed of E. Brum Negreiros, president; Nelson Passarelli, Paulo Dias da Costa, and F. J. de Silveira Lobo, Jr., vice presidents; U. Fabiano Alves, secretary-general; Haroldo Cardoso de Castro, treasurer; and a scientific council composed of Ernesto Mendes, president, Eduardo Rabello, A. Oliveira Lima, Mario Pinto de Miranda, C. Cruz Lima, Antar Padilha Goncalves, J. B. Grecco, and Lain Pontes de Carvalho.

The officers and directors of the International Association of Allergology for 1951-1955, who served during this second congress were: Fred W. Wittich, Minneapolis, Minnesota, president; Samuel M. Feinberg, Chicago, Illinois, president-elect; Ulysses Fabiano Alves, Rio de Janeiro, Brazil, first vice president; Pasteur Vallery-Radot, Paris, France, second vice president; David Williams, Cardiff, Wales, third vice president; Bernard N. Halpern, Paris, France, secretary-general; A. S. Grumbach, Zurich, Switzerland, treasurer; C. G. Loeffler, Zurich, Switzerland, past president; and Ethan Allan Brown, Boston, Massachusetts, Egon Bruun, Copenhagen, Denmark, M. S. Mallen, Mexico City, Mexico, and Francis Rackemann, Boston, Massachusetts, members-at-large, board of directors.

About four hundred registrants, representing thirty-three national allergy societies, participated. The congress was formally opened on Sunday afternoon, November 6, with words of welcome from the Brazilian Allergy Society, the Brazilian Commissioner of Education, representing the Brazilian government, and the officers of the Association. This was followed by presentation of the honorary guest speakers, who addressed the delegates. The evening was given over to a social program. Monday morning was devoted to a series of concomitant sectional meetings on histamine and the pathogenesis of allergic reaction, drug allergy, immunology and allergy, and immunology, with the afternoon taken up with numerous sectional meetings on immunology, asthma, and dermatologic allergy. On Tuesday morning a symposium on dermatologic allergy was held, at which the speakers were Louis Schwartz, U.S.A.; Hans Storck, Switzerland; S. Hellerstrom, Switzerland; and Jacques Charpy, France. A symposium on histamine filled the entire afternoon, and W. Schayer, U.S.A.; E. A. Zeller, U.S.A.; B. Halpern, France; M. Rocha e Silva, Brazil; and Bram Rose, Canada, spoke. An immunology and allergy symposium was conducted on Wednesday morning by E. A. Kabat, H. Sherwood Lawrence, J. Freund, and M. Loveless, all of the United States, and the afternoon program consisted of a symposium on drug allergy, at which the speakers were: E. A. Brown, S. M. Feinberg, and R. L. Mayer, all of the United States, and A. S. Esselier of Switzerland.

OFFICERS AND DIRECTORS OF THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY, 1956-1958

Seated: Jose Quintero Fossas, Havana, Cuba, secretary-general; Guido Ruiz Moreno, Buenos Aires, Argentina, first vice president; Samuel M. Feinberg, Chicago, Illinois, president; Bernard N. Halpern, Paris, France, president-elect; and Bram Rose, Montreal, Canada, second vice president. *Standing:* Paulo Dias da Costa, Rio de Janeiro, Brazil; Howard Osgood, Buffalo, New York; and Ethan Allan Brown, Boston, Massachusetts, members-at-large, board of directors; and Fred W. Wittich, Minneapolis, Minnesota, past president.

Not Present: Egon Bruun, Copenhagen, Denmark, treasurer; Umberto Serafini, Rome, Italy, third vice president; and David Williams, Cardiff, Wales, member-at-large, board of directors.

In the late afternoon, another symposium was held at which the subject of allergy and the hormones was discussed by L. H. Ballestero, Argentina; S. Yrarrazaval, Chile; and Z. Eriksson-Lihr, Finland. An asthmatic patient symposium was held on the morning of November 10, at which M. Samter, F. W. Wittich, J. Sheldon, and S. Hampton of the U.S.A., and C. Jimenez Diaz, Spain, and G. Ruiz Moreno, Argentina, discussed this subject. The subject of leprosy and tuberculosis was covered by F. E. Rabello, Brazil; J. M. Fernandez, Argentina; J. Rosemberg, Brazil; and N. Souza Campos, Brazil, in a symposium on Friday morning, and in the afternoon therapeutics in allergy was discussed by L. Unger and C. Arbesman, U.S.A., U. Serafini, Italy; and B. Rose, Canada. More than 250 papers were presented at the symposia and the sectional meetings. The sectional meetings Friday afternoon covered leprosy and tuberculosis, treatment, and miscellaneous subjects, and on Saturday morning hormonal allergy and miscellaneous subjects.

At the official banquet Wednesday evening, the president; Dr. Fred W. Wittich, was presented with a scroll by the Brazilian Allergy Society, also signed by representatives of all countries present, in appreciation of his services as president and his contributions to the development of allergy throughout the world.

After the sectional meetings on Saturday morning, the congress officially closed on Saturday afternoon with the seating of the new officers and board of directors (see photograph). The next congress will be held in the late fall of 1958 in Paris.

In Memoriam

RALPH BOWEN

It is with deep regret that we announce the death on January 31, 1956, of an outstanding Fellow of the College, Dr. Ralph Bowen of Houston, Texas.

Dr. Bowen was born in Iowa, July 4, 1898. He received his B.S. degree in 1921 and his M.D. degree in 1924 from the Iowa State University. Subsequently, he did postgraduate work at Harvard and Washington universities, and later he studied under Dr. George Bray in London. He was certified by the American Board of Pediatrics in 1936.

Dr. Bowen entered the practice of allergy in Houston in 1939. Shortly after The American College of Allergists was organized, it was incorporated in the State of Minnesota, and Dr. Bowen became vice president, a position which he held for about one year. He was a co-founder of the International Correspondence Society of Allergists and assisted actively in publication of the Letters.

Dr. Bowen was also a Fellow of the American Academy of Allergy, a member of the Southwest Allergy Forum and one of its past presidents, and a former chairman of the Allergy Section of the Southern Medical Association. He was a lecturer in pediatrics at The University of Texas Medical Branch, Associate Professor of Medicine at Baylor University College of Medicine, and Chief of the Allergy Service at the Texas Children's Hospital. He was the author of numerous articles on allergy, one of which, "Gamma Globulin and Its Therapeutic Value in the Asthmatic Child," will be given posthumously at the Southwest Allergy Forum in April.

Dr. Bowen is survived by his widow, Mrs. Celestine Bowen; a daughter, Judy Bowen; and one son, Dr. Ralph Bowen, Jr.; his parents, Mr. and Mrs. Leonard Bowen of Muscatine, Iowa; one sister, and three brothers.

The Ralph Bowen Memorial for Asthmatic Children has been established at the Texas Children's Hospital in Houston.

AMERICAN MEDICAL WRITERS' ASSOCIATION NUMBER OF MISSISSIPPI VALLEY MEDICAL JOURNAL

The January issue of the *Mississippi Valley Medical Journal* is the annual American Medical Writers' Association number of the publication. It contains twelve papers read at the annual meeting of the writers' association held at St. Louis in September, 1955, and also includes three talks given at the A.M.W.A. workshop on medical writing, the two winning essays in the 1955 Mississippi Valley Medical Society Essay Contest, and an index of all the principal references pertaining to medical writing from 1948-1955. As in previous years, all the A.M.W.A. papers, plus the references on medical writing, have been incorporated into a booklet which is available for twenty-five cents, postpaid, from the A.M.W.A. headquarters, W.C.U. Building, Quincy, Illinois.

BOOK REVIEWS

YEAR BOOK OF MEDICINE (1955-56 Year Book Series). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. 711 pages, including index. Chicago: The Year Book Publishers, Inc., 1955. Price, $6.00.

Each year a completely new Year Book of Medicine appears to help the busy physician organize his reading and increase his efficiency and knowledge. The current volume follows the same pattern as in former years, with the contents divided into the general subjects of infections, the chest, the blood and blood-forming organs, the heart and blood vessels and the kidney, the digestive system, and metabolism, with an editor for each section who selects, abstracts, and evaluates the outstanding articles from the current literature and makes pertinent and authoritative comments upon them.

This volume presents synopses of 521 recent articles taken from the leading American and foreign medical journals from May, 1954, to May, 1955, reports on 250 disease entities, contains 244 new or improved treatment measures and 233 of the latest diagnostic procedures, all accompanied by interesting case reports and clinical and experimental studies. Among the new developments included are: renal disease apparently caused by hormonal allergy, alternating bradycardia and tachycardia, new diagnostic sign in rubella, new serum proteins, torulosis, mumps and infertility, new oily medium for bronchography, change in response to CO_2 inhalation in emphysema, pulmonary aspects of periarteritis nodosa, prevention of atelectasis, polycythemia, accquired hemolytic anemia, chronic hyperventilation, and primary aldosteronism as a new clinical syndrome. Photographs, charts, and graphs are included.

As in past years, this Year Book of Medicine will provide the diagnostician and clinician with the latest information in capsule form on a variety of subjects with which he will want to keep abreast.—V.E.S.

ALLERGY AND ANAPHYLAXIS. Keizo Nakamura, M.D., Professor of Bacteriology, Nippon Medical School, Tokyo, Japan, and Chief, Department of Serology, National Institute of Health, Tokyo, Japan. 114 pages, illus. Published by Department of Bacteriology, Nippon Medical School, Tokyo, Japan.

This monograph represents the results of twenty years' study of allergy and anaphylaxis on the part of the author and his co-workers, and is of paramount importance to those who read the English language, as it presents the subject in very clear English throughout. It contains five chapters, subdivided into sections, thirty-five figures, and thirty tables.

The first chapter on "Anaphylaxis and Immunity" represents observations on toxin-anaphylaxis *in vitro* and *in vivo*, and the mechanism of antitoxic immunity, particularly the significance of antitoxin in the circulating blood and tissues in active immunity. In the second chapter succinct coverage is given to the fundamental factors relating to the mechanism of anaphylaxis. The third chapter deals with the histamine and acetylcholine theory in anaphylaxis in all of its phases, including experimental studies and research, and a detailed description of the effective substance proved in anaphylaxis. It presents the relation between organic phosphoric acid and anaphylaxis and the influence of pharmacodynamic antagonists in anaphylaxis, especially the effect of atropine, phenylurethan and d-arginine on

(Continued on Page A-34)

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*Study of 50 children: Dees, S. C., et al., Ann. Allergy, *11*:297, 1953.

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(Continued from Page 120)

the anaphylactic reaction. An entire chapter is devoted to allergy and the anti-allergy drugs, covering studies on antihistaminic and anti-acetylcholine drugs.

The comprehensive research and intensive study represented by this compact monograph make it an essential reference book for all physicians and students interested in the subject and its development through the years. The literature cited covers eighty-eight references.—F.W.W.

RHEUMATOID ARTHRITIS AND PSORIASIS VULGARIS. Internal and Cutaneous Manifestations of the Permanent Endoparasitism in the Homo Sapiens, Their Common Etiology, Pathogenesis, and Specific Vaccine Therapy. Tibor Benedek, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Stritch School of Medicine, Loyola University, Chicago, Illinois. 308 pages, illus. Ann Arbor, Michigan: Edwards Brothers, Lithoprinters, 1955. (For further information address the author at 25 East Washington Street, Chicago 2, Illinois.) Distributed by Chicago Medical Book Company, Jackson & Honore Streets, Chicago 12, Illinois.

This book presents the results and conclusions of the research and clinical experience of the author. Whether or not one agrees with his conclusions, it should be read and considered by every one interested in rheumatoid arthritis and psoriasis vulgaris.

The author believes that he has shown that the specific cause of these clinical conditions is an organism which he has named *Bacillus endoparasiticus Benedek* and that it is a permanent endoparasite of "homo sapiens." When the individual becomes allergic to this bacillus and the shock tissue is cutaneous, then that person develops psoriasis or one of its variables; when the shock tissue is joint tissue, then he develops rheumatoid arthritis. Food and drug allergies aggravate the condition by causing "an outpouring of these parasites into the sensitized connective tissue." Several chapters are devoted to consideration of the various theories of the etiology and the treatment of arthritis and psoriasis and why none of them are adequate or acceptable.

Some bacteriologists believe that the *Bacillus endoparasiticus Benedek* is none other than *Bacillus megatherium* which is found in water, soil, and as a contaminant of cultures. It is ranked by many in the subtilis group. These facts, plus his method of isolation of the organism, are some of the weaknesses of his thesis. Either the O or S type of culture are used for vaccine preparation. Because the bacillus is a spore former, the vaccine is sterilized by boiling for one hour on each of three consecutive days. The question could be raised, what does all this heating do to the specificity of the bacterial antigen, and whether its use is any more than another type of nonspecific therapy.—G.E.R.

CONNECTICUT ALLERGY SOCIETY

At the annual meeting of the Connecticut Allergy Society held January 11, 1956, the following officers were elected: president, Paul Winer, New Haven; vice president, George Hurwitz, Hartford; secretary-treasurer, Frederick Kessler, New Haven; executive committee, V. P. Cenci, Hartford, and Russell Webber and Sidney Jennes, Waterbury.